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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Tibotec Pharmaceuticals Ltd.
Unit 4, Block 4B, Blanchardstown Corporate
Park
Blanchardstown, Dublin 15
IRLANDE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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5- OR 6-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS INHIBITORS OF RESPIRATORY SYNCYTIAL VIRUS REPLICATION

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5- OR 6-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS INHIBITORS OF RESPIRATORY SYNCYTIAL VIRUS REPLICATION

The present invention is concerned with 5- or 6-substituted-benzimidazole derivatives having antiviral activity, in particular, they have an inhibitory activity on the replication of the respiratory syncytial virus (RSV). It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumovirinae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

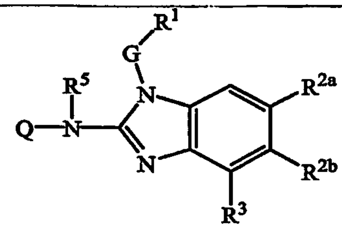
Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. A first one is ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drugs, RespiGam® and palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases enhanced disease during subsequent infection. Life attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

Previously, benzimidazoles and imidazopyridines as inhibitors of RSV replication have been described in WO 01/00611, WO 01/00612 and WO 01/00615.

The present invention now concerns inhibitors of RSV replication and are defined as the compounds of formula (I)

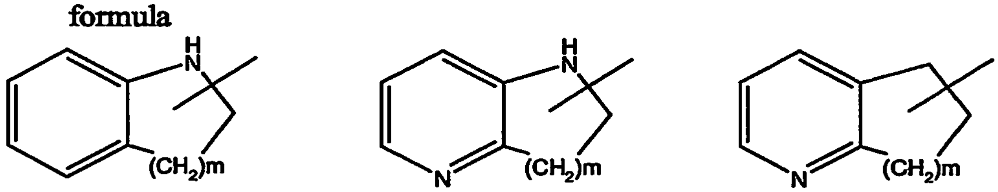


their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms wherein

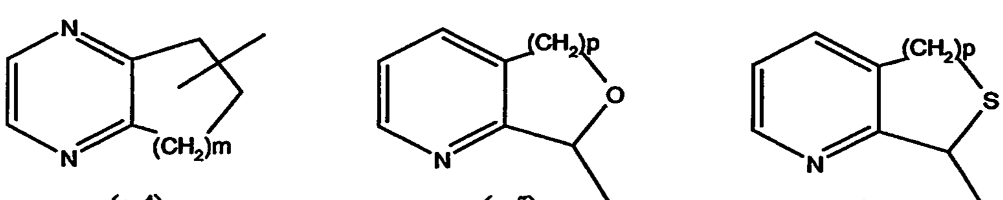
Q is Ar^2, R^6, pyrrolidinyl substituted with R^6, piperidinyl substituted with R^6 or homopiperidinyl substituted with R^6,

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one or more substituents individually selected from the group consisting of hydroxy, C_{1-6}alkyloxy, Ar^1C_{1-6}alkyloxy, C_{1-6}alkylthio, Ar^1C_{1-6}alkylthio, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$ and Ar^1C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$;

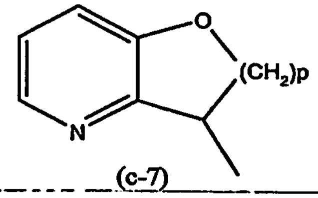
R^1 is Ar^1 or a monocyclic or bicyclic heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-b]pyridyl or a radical of formula



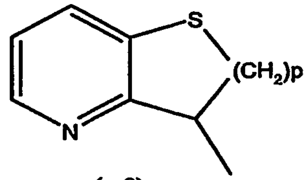
(c-1) (c-2) (c-3)



(c-4) (c-5) (c-6)



(c-7)



(c-8) ;

wherein each of said monocyclic or bicyclic heterocycles may optionally be substituted with 1 or where possible more, such as 2, 3, 4 or 5, substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

one of R^{2a} and R^{2b} is cyanoC_{1-6}alkyl, cyanoC_{2-6}alkenyl, Ar^3C_{1-6}alkyl, Het^1C_{1-6}alkyl, $N(R^{8a}R^{8b})C_{1-6}$alkyl, Ar^3C_{2-6}alkenyl, Het^1C_{2-6}alkenyl, Ar^3aminoC_{1-6}alkyl, Het^1aminoC_{1-6}alkyl, Ar^3thioC_{1-6}alkyl, Het^1thioC_{1-6}alkyl, Ar^3sulfonylC_{1-6}alkyl, Het^1sulfonylC_{1-6}alkyl, Ar^3aminocarbonyl, Het^1aminocarbonyl, $Ar^3(CH_2)_n$aminocarbonyl, $Het^1(CH_2)_n$aminocarbonyl, Ar^3carbonylamino, Het^1carbonylamino, $Ar^3(CH_2)_n$carbonylamino, $Het^1(CH_2)_n$carbonylamino, and the other one of R^{2a} and R^{2b} is hydrogen;

in case R^{2a} is hydrogen, then R^3 is hydrogen;

in case R^{2b} is hydrogen, the R^3 is hydrogen or C_{1-6}alkyl;

R^{4a} and R^{4b} can be the same or can be different relative to one another, and are each independently hydrogen or C_{1-6}alkyl; or

R^{4a} and R^{4b} taken together may form a bivalent radical of formula -$(CH_2)_s$- wherein s is 4 or 5;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is hydrogen or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of trifluoromethyl, $NR^{7a}R^{7b}$, C_{3-7}cycloalkyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, Ar^2-thio-, $Ar^2(CH_2)_n$oxy, $Ar^2(CH_2)_n$thio, hydroxycarbonyl, aminocarbonyl, C_{1-4}alkyl-carbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, $Ar^2(CH_2)_n$carbonyl, amino-carbonyloxy, C_{1-4}alkylcarbonyloxy, Ar^2carbonyloxy, $Ar^2(CH_2)_n$carbonyloxy, C_{1-4}alkoxycarbonyl$(CH_2)_n$oxy, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, aminosulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl or a heterocycles selected from the group consisting of

pyrrolidinyl, pyrrolyl, dihydropyrrolyl, thiazolidinyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, wherein each of said heterocycle may optionally be substituted with oxo or C_{1-6}alkyl;

R^{7a} is hydrogen, C_{1-6}alkyl, formyl or C_{1-6}alkylcarbonyl;

R^{7b} is hydrogen, C_{1-6}alkyl, formyl or C_{1-6}alkylcarbonyl;

R^{8a} is C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^3C_{1-6}alkyl, Het^1C_{1-6}alkyl;

R^{8b} is C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^3C_{1-6}alkyl, Het^1C_{1-6}alkyl;

each n independently is 1, 2, 3 or 4;

each m independently is 1 or 2;

each p independently is 1 or 2;

Ar^1 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

Ar^2 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from the group consisting of halo, hydroxy, amino, cyano, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy, aminosulfonyl, aminocarbonyl, hydroxycarbonyl, C_{1-4}alkylcarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl and C_{1-4}alkoxycarbonyl;

Ar^3 is phenyl, naphthalenyl, 1,2,3,4-tetrahydro-naphthalenyl or indanyl, wherein said phenyl, naphtyl, 1,2,3,4-tetrahydro-naphthalenyl or indanyl may optionally and each individually be substituted with one or more, such as 2, 3 or 4, substituents selected from the group consisting of halo, hydroxy, mercapto, amino, cyano, C_{1-6}alkyl, Ar^1, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1-oxy, aminosulfonyl, aminocarbonyl, hydroxycarbonyl, C_{1-4}alkylcarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-4}alkylcarbonylamino and C_{1-4}alkoxycarbonyl;

Het^1 is a heterocycle being selected from tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidinonyl, furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, tetrahydroquinolinyl, quinolinyl, isoquinolinyl, benzodioxanyl, benzodioxolyl, indolinyl, indolyl, each of said heterocycle may

optionally be substituted with oxo, amino, Ar^1, C_{1-4}alkyl, aminoC_{1-4}alkyl, Ar^1C_{1-4}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)amino.

The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated. Prodrugs are characterized by a good aqueous solubility and bioavailability, and are readily metabolized into the active inhibitors *in vivo*.

As used herein C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl and the like; C_{2-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like.

As used herein C_{2-6}alkenyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having at least one double bond and having from 2 to 6 carbon atoms such as ethenyl, propenyl, buten-1-yl, buten-2-yl, penten-1-yl, penten-2-yl, hexen-1-yl, hexen-2-yl, hexen-3-yl, 2-methylbuten-1-yl and the like. C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

C_{2-5}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl and the like, C_{1-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like; C_{1-10}alkanediyl is meant to include C_{1-6}alkanediyl and the higher homologues thereof

having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. The term (=N-OH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC_{1-4}alkyl, they may be the same or different.

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable.

Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable occurs more than one time in any constituent, each definition is independent.

Whenever used hereinafter, the term "compounds of formula (I)", or "the present compounds" or similar term is meant to include the compounds of general formula (I), their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms. An interesting subgroup of the compounds of formula (I) or any subgroup thereof are the *N*-oxides, salts and all the stereoisomeric forms of the compounds of formula (I).

It will be appreciated that some of the compounds of formula (I) may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess.

Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

For some of the compounds of formula (I), their prodrugs, N-oxides, salts, solvates, quaternary amines, or metal complexes and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complexating properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Interesting compounds are those compounds of formula (I) or any subgroup thereof wherein G is C_{1-10}alkanediyl; more in particular, G is methylene.

Other interesting compounds are those compounds of formula (I) or any subgroup thereof wherein R^1 is pyridyl optionally substituted with 1 or 2 substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O$)_n$-, halo(-CH_2-CH_2-O$)_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O$)_n$-,

$Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$- and mono-or di($C_{1-6}$alkyl)amino($-CH_2-CH_2-O)_n$-; more in particular R^1 is pyridyl substituted with hydroxy and C_{1-6}alkyl.

Preferred compounds are those compounds listed in tables 1 through 5, more in particular the compound numbers 1 to 77, 140 to 162 and 168 to 174.

Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions, comprising those described hereinafter.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said

compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV).

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I) or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the RSV infection.

The present invention also relates to the use of the present compounds or any subgroup thereof in the manufacture of a medicament for the treatment or the prevention of viral infections, particularly RSV infection.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms

depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.
Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I) and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage.

Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

In general it is contemplated that an antivirally effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

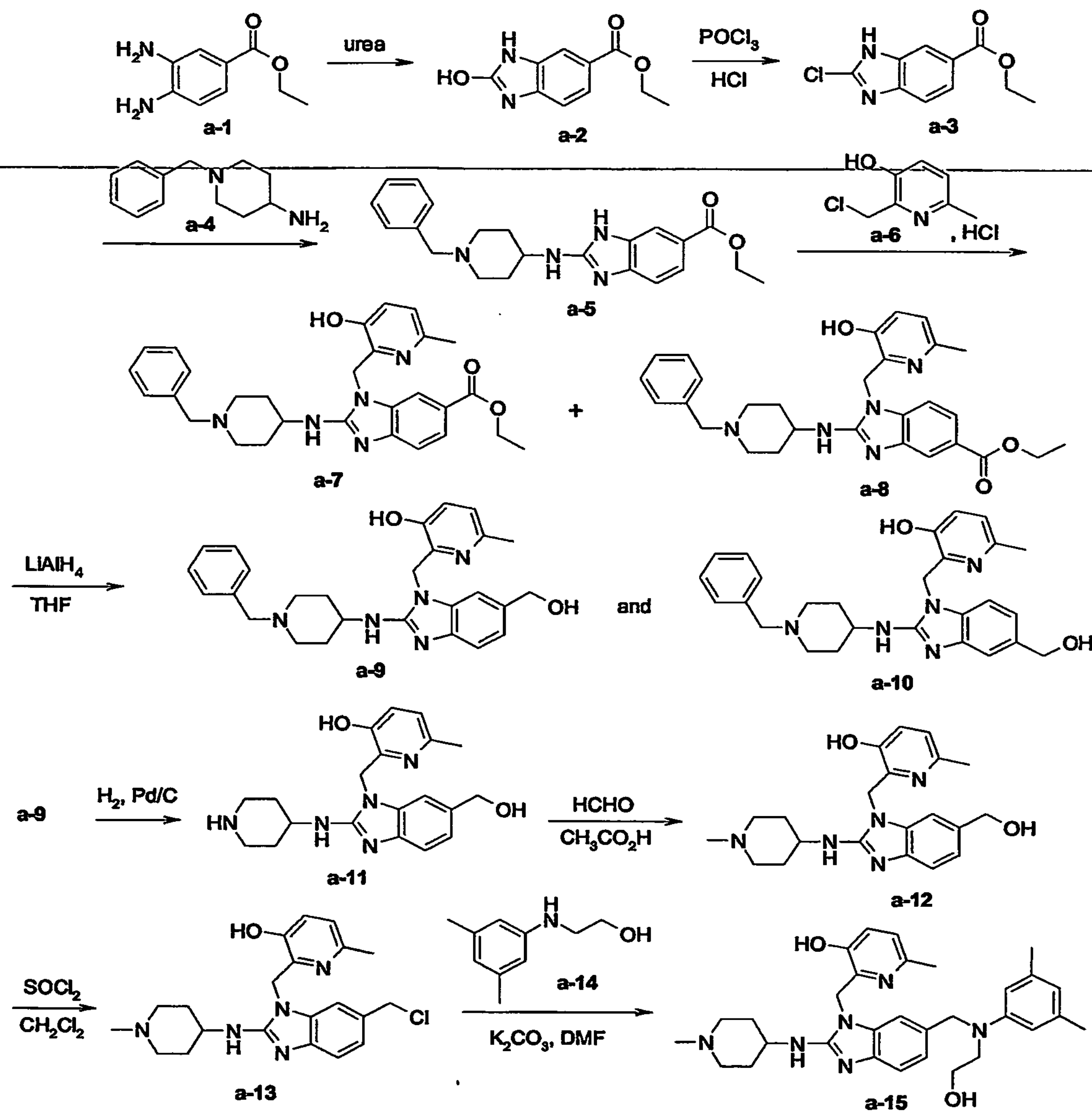
Also, the combination of another antiviral agent and a compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections.

Experimental Part

The following examples are intended to illustrate the present invention.

A. Chemical synthesis of the compounds of formula (I)

Scheme A



A mixture of a-1 (0.166 mol) and urea (0.199 mol) in xylene (300 ml) was stirred under reflux for 12 hours. The reaction was cooled down to room temperature. The precipitate was filtered off, rinsed with xylene and diisopropylether, and then dried, yielding 32g of intermediate a-2 (93%, melting point: > 260°C).

A mixture of a-2 (0.073 mol) in $POCl_3$ (150 ml) was stirred at 100°C. HCl conc. (around 1.5 ml) was added drop wise very carefully until the dissolution of a-2. The mixture was stirred at 120°C for 6 hours. The solvent was evaporated till dryness. The residue was taken-up in H_2O/ice, basified with K_2CO_3 (powder) and extracted with ethylacetate + 10% methanol. The organic layer was separated, dried (over $MgSO_4$),

filtered and the solvent was evaporated till dryness, yielding 13.5 g of intermediate **a-3** (83%, melting point: 178°C).

A mixture of **a-3** (0.051 mmol) and **a-4** (0.056 mol) was stirred at 160°C for 2 hours. The residue was taken-up in CH_2Cl_2/H_2O and basified with a 10% solution of K_2CO_3 in water. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/methanol/NH_4OH 95/5/0.5). The pure fractions were collected and the solvent was evaporated, yielding 15.3 g of intermediate **a-5** (79%).

A mixture of **a-5** (0.0396 mol), **a-6** (0.059 mol) and K_2CO_3 (0.1584 mol) in CH_3CN (180ml) was stirred and refluxed for 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2. The organic layer was washed with H_2O, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (20g) was purified by column chromatography over silica gel (eluent: Toluene/2-propanol/ NH_4OH 85/15/1; 20-45µm). Two fractions were collected and the solvent was evaporated, yielding 5.3g of fraction 1 (27%) and 6.3g of fraction 2 (32%). Fraction 1 was crystallized twice in 2-propanone/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 4.9g of intermediate **a-7** (25%, melting point: 179°C). Fraction 2 was crystallized from 2-propanone/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 5.5g of intermediate **a-8** (28%, melting point: 238°C).

$LiAlH_4$ (0.009 mol) was added portion wise to a mixture of **a-7** (0.003 mol) in tetrahydrofuran (60 ml) at 5°C under N_2 flow. The reaction was stirred at 5°C for 1 hour and then at room temperature for 12 hours. Ethylacetate and H_2O were added carefully and the aqueous layer was saturated with K_2CO_3 (powder). The organic layer was separated, dried (over $MgSO_4$) and then filtered over celite. The filtrate was evaporated till dryness, yielding 1.3 g of intermediate **a-9** (97%). The crude product was used directly in the next reaction step.

Intermediate **a-10** was prepared analogously to the procedure described for intermediate **a-9**.

A mixture of **a-9** (0.0028 mol) and Pd/C 10% (2.5g) in CH_3OH (40ml) was hydrogenated at 40°C for 12 hours under an 8 bar pressure, then filtered over celite. Celite was washed with a solution of CH_3OH/tetrahydrofuran (50/50). The filtrate was evaporated till dryness, yielding 1.8g of intermediate **a-11** (95%, melting point: 260°C).

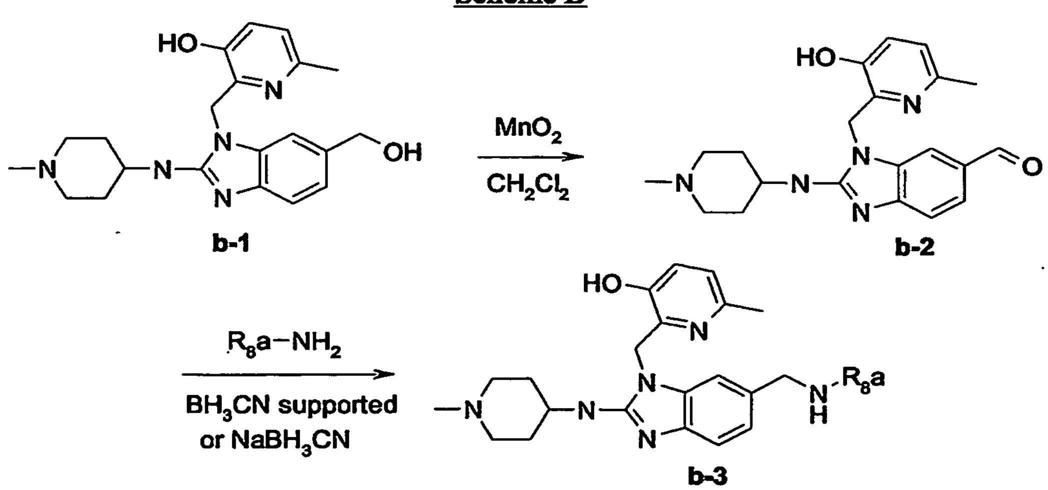
CHOH 37% in water (0.0098 mol), $NaBH_3CN$ (0.0059 mol) then CH_3CO_2H (2ml) were

added at room temperature to a mixture of **a-11** (0.0049 mol) in CH_3CN (50ml). The mixture was stirred at room temperature for 12 hours. The solvent was evaporated till dryness. The residue was taken up in ethanol (30ml) and a 5N solution of HCl in 2-propanol (4ml) was added. The mixture was stirred at 80°C for 8 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2/K_2CO_3 10%. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was crystallized from CH_3OH/2-propanone/ CH_3CN. The precipitate was filtered off and dried, yielding 1.65g of **a-12** (88%). Part of this fraction (0.15g) was crystallized from CH_3OH/2-propanone. The precipitate was filtered off and dried (melting point: 165°C).

$SOCl_2$ (2.1ml) was added drop wise to a mixture of **a-12** (0.0018 mol) in CH_2Cl_2 (20ml) at 5°C. The mixture was stirred at 5°C for 1 hour, then at room temperature for 12 hours. The solvent was evaporated till dryness, yielding 0.93g of intermediate **a-13** (100%). The crude product was used directly in the next reaction step.

A mixture of **a-13** (0.0003 mol), **a-14** (0.0005 mol) and K_2CO_3 (0.0019 mol) in dimethylformamide (30ml) was stirred at 80°C for 4 hours and poured out into H_2O. The aqueous layer was saturated with K_2CO_3 and extracted with CH_2Cl_2/CH_3OH. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.25g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/1; 10μm). The pure fractions were collected and the solvent was evaporated. The residue (0.05g, 24%) was crystallized from 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.042g of compound **a-15** (20%, melting point: 176°C).

<u>Scheme B</u>

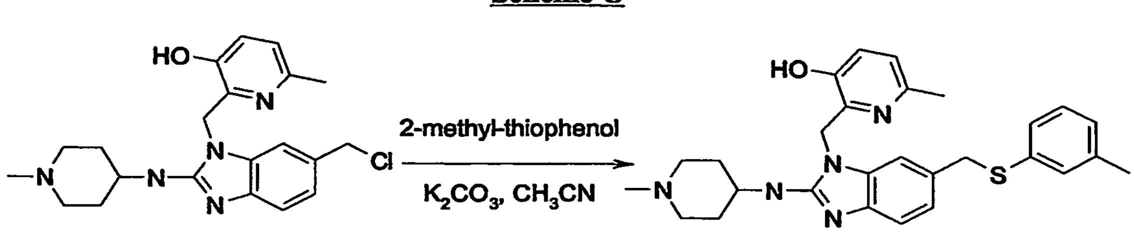


A mixture of **b-1** (0.0028 mol) and MnO_2 (2.5g) in CH_2Cl_2 (40ml) was stirred at room temperature for 12 hours, and then filtered over celite. Celite was rinsed with CH_2Cl_2. The filtrate was evaporated till dryness. The residue was taken up in 2-propanone. The precipitate was filtered off and dried, yielding 0.75g of intermediate **b-2** (69%, melting point: 250°C).

Pathway 1 : A mixture of **b-2** (0.0001 mol), 3,5-dichloro aniline (0.0001 mol), BH_3CN on solid support (0.0001 mol) and CH_3CO_2H (2 drops) in CH_3OH (4ml) was stirred at room temperature for 24 hours. The solution was filtered. The filtrate was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 87/12/1.5; 5μm). The pure fractions were collected and the solvent was evaporated, yielding 0.026g of 2-[6-[(3,5-dichloro-phenylamino)-methyl]-2-(1-methyl-piperidin-4-ylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (38%).

Pathway 2 : b-2 (0.0005 mol), $NaBH_3CN$ (0.0006 mol), and then CH_3CO_2H (0.2ml) were added at room temperature to a mixture of 3-methyl-aniline (0.0006 mol) in CH_3CN (20ml). The mixture was stirred at room temperature for 12 hours. H_2O was added. The mixture was saturated with K_2CO_3 (powder) and extracted with CH_2Cl_2/CH_3OH. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.3g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/triethylamine; 90/10/0.1; 5μm). The pure fractions were collected and the solvent was evaporated. The residue (0.17g, 68%) was crystallized from CH_3OH/2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.13g of 2-[6-[(1-ethylidene-3-methyl-penta-2,4-dienylamino)-methyl]-2-(1-methyl-piperidin-4-ylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (52%, melting point: 141°C).

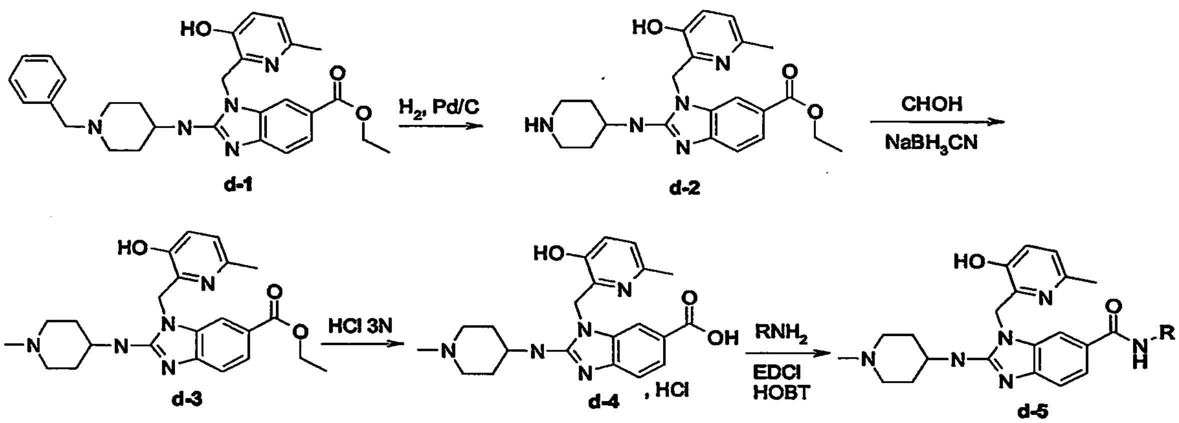
<u>Scheme C</u>



A mixture of **c-1** (0.0018 mol), 2-methyl-thiophenol (0.002 mol) and K_2CO_3 (0.0077 mol) in CH_3CN (70ml) was stirred at 50°C for 12 hours. The solvent was evaporated till dryness. The residue was taken up in H_2O. The mixture was extracted with CH_2Cl_2.

The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.55g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 88/12/2; 15-40µm). The pure fractions were collected and the solvent was evaporated. The residue (0.35g, 39%) was crystallized from CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.32g of 6-methyl-2-[2-(1-methyl-piperidin-4-ylamino)-6-m-tolylsulfanyl-methyl-benzoimidazol-1-ylmethyl]-pyridin-3-ol (melting point: 202°C).

Scheme D



In scheme D, R is defined as Ar[3], Het[1], Het[1]$(CH_2)_n$ or Het[1]$(CH_2)_n$.

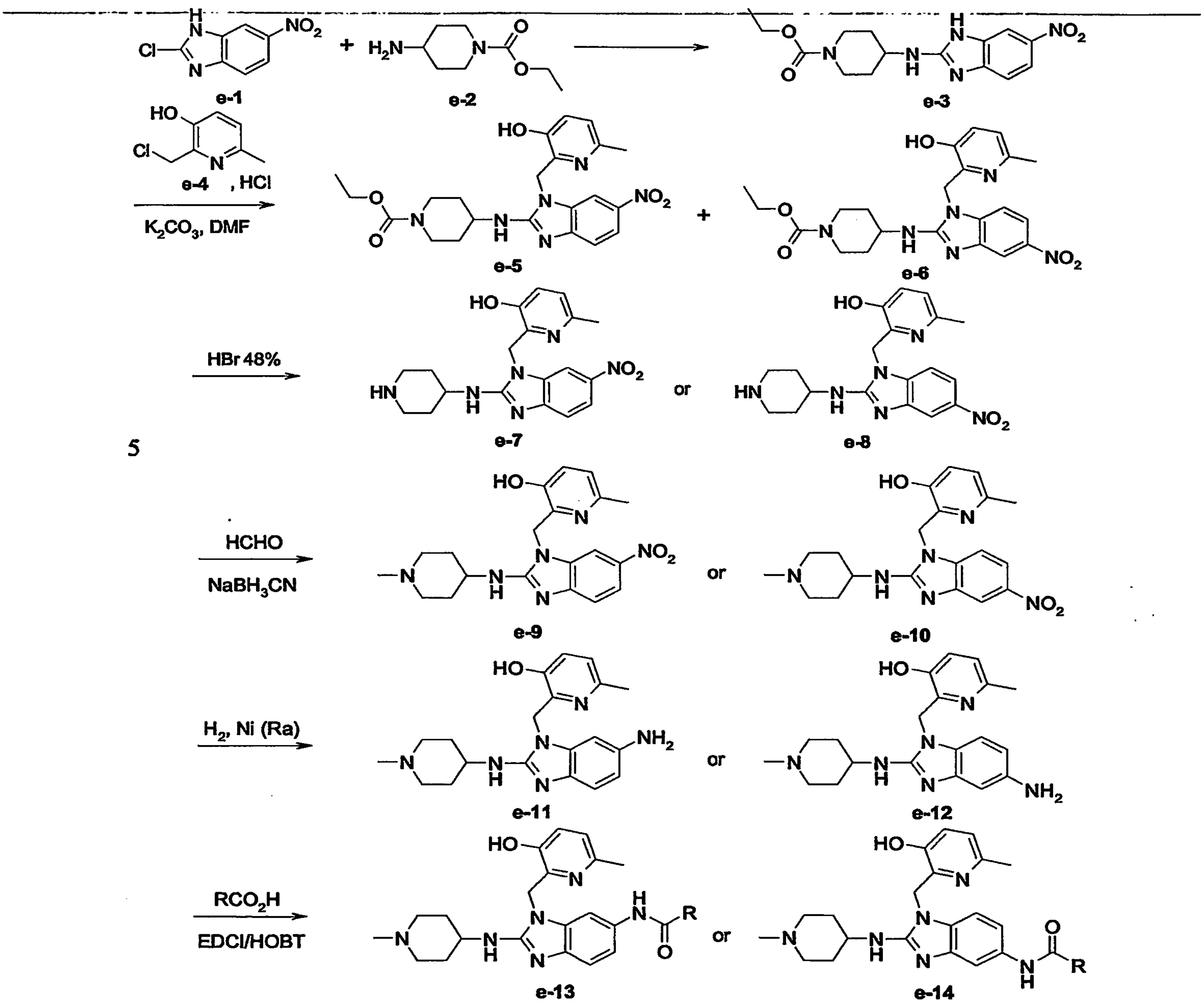
Intermediate **d-2** (melting point: 262°C)was prepared analogous to the procedure described for intermediate **a-11.** Intermediate **d-3** was prepared analogous to the procedure described for intermediate **a-12.**

A mixture of **d-3** (0.0003 mol) in a 3N solution of HCl in water (30ml) was stirred at 80°C for 12 hours. The solvent was evaporated. The residue was dried, yielding 0.18g of intermediate **d-4**. The crude product was used directly in the next reaction step.

A mixture of **d-4** (0.0003 mol), 2-methyl-aniline (0.0005 mol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.0005 mol) and 1-hydroxybenzotriazole (0.0005 mol) in CH_2Cl_2 (20ml) was stirred at room temperature for 24 hours. A 10% solution of K_2CO_3 in water was added. The aqueous layer was saturated with K_2CO_3 (powder). The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.2g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 80/20/1; 10µm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.29g (14%). This fraction was taken up in diisopropylether, then CH_3OH/diisopropylether. The

precipitate was filtered off and dried, yielding 0.007g of 3-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-2-(1-methyl-piperidin-4-ylamino)-3H-benzoimidazole-5-carboxylic acid m-tolylamide (4%, melting point: 172°C).

Scheme E



A mixture of e-1 (0.0524 mol) and e-2 (0.1048 mol) was stirred at 120°C in a Parr pressure vessel for 10 hours, then taken up into H_2O and extracted with ethylacetate. The separated organic layer was purified by short open column chromatography over

silica gel (eluent: CH_2Cl_2/methanol 96/4). The product fractions were collected and the solvent was evaporated till dryness, yielding 7.7g of intermediate **e-3** (44%).

A mixture of **e-3** (0.0312 mol), **e-4** (0.0343 mol) and K_2CO_3 (0.1092 mol) in dimethylformamide (100ml) was stirred at 70°C for 24 hours. H_2O was then added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (12.2g) was purified by column chromatography over silica gel (eluent: toluene/isopropanol/NH_4OH 90/10/0.5; 15-40μm). Two fractions were collected and the solvent was evaporated, yielding 4g of intermediate **e-5** (28%) and 5.4g of intermediate **e-6** (38%).

e-5 (0.0088 mol) was added portion wise to a 48% solution of HBr in water (40ml). The mixture was brought slowly to 70°C, and then stirred for 12 hours. The precipitate was filtered, washed with CH_3CN and dried. The residue (4.6g, 80%) was taken up in H_2O and basified with K_2CO_3 (powder). The precipitate was filtered, and then washed with ethanol. The filtrate was evaporated, yielding 3g of intermediate **e-7** (52%). In an analogous way, e-8 was prepared

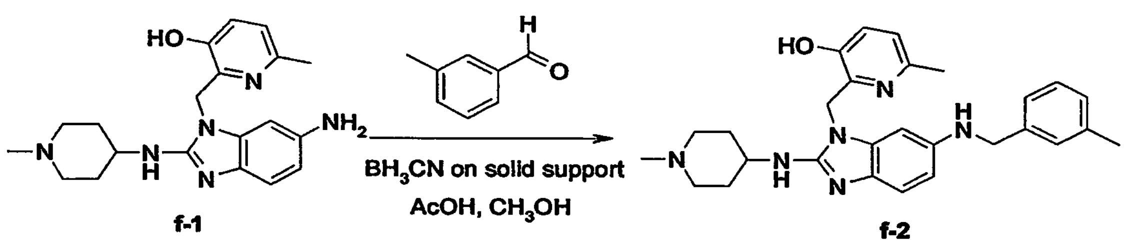
HCHO 37% in H_2O (0.0152 mol) then $NaBH_3CN$ (0.0091 mol) were added at room temperature to a mixture of **e-7** (0.0075 mol) in CH_3CN (100ml). Acetic acid (3.5ml) was added slowly at room temperature. The mixture was stirred at room temperature for 12 hours and poured out into H_2O. The aqueous layer was saturated with K_2CO_3 (powder). The mixture was extracted with ethylacetate/CH_3OH. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness, yielding 2.6g of intermediate **e-9** (87%). In an analogous way, **e-10** was prepared.

A mixture of **e-9** (0.0065 mol) and Raney Nickel (2.6g) in CH_3OH (100ml) was hydrogenated at room temperature for 1 hour under a 3 bar pressure, and then filtered over celite. Celite was washed with CH_3OH. The filtrate was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 85/14/1; 15-40μm). The pure fractions were collected and the solvent was evaporated, yielding 0.85g of intermediate **e-11** (35%). In an analogous way, **e-12** was prepared.

A mixture of **e-11** (0.000125 mol) and 3-methyl-benzoic acid (0.00025 mol) in CH_2Cl_2 (4 ml) was stirred at room temperature. 1-hydroxybenzotriazole (0.00025 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.00025 mol) were added. The reaction was stirred at room temperature for 12 hours. The solution was

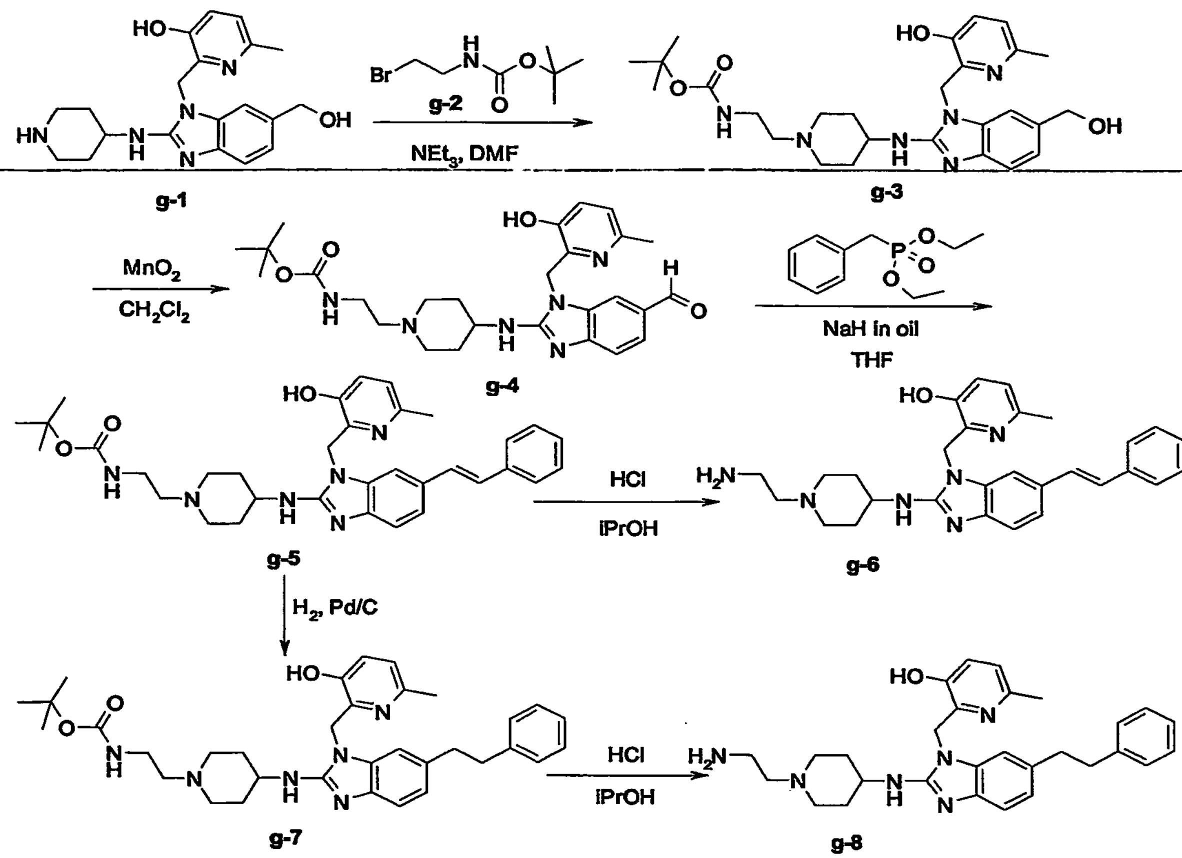
concentrated and a 10% solution of $NaHCO_3$ in water (2 ml) and CH_3OH (2 ml) were added. The mixture was stirred and refluxed for 4 hours. CH_3OH was then removed under reduced pressure and the resulting solution extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.5; 15-40µm). The pure fractions were collected and the solvent was evaporated, yielding 0.04g of N-[3-(3-hydroxy-6-methyl-pyridin-2-yl-methyl)-2-(1-methyl-piperidin-4-ylamino)-3H-benzoimidazol-5-yl]-3-methyl-benzamide (60%). In an analogous way, N-[1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-2-(1-methyl-piperidin-4-ylamino)-1H-benzoimidazol-5-yl]-3-methyl-benzamide (0.028 g or 42% yield) was prepared.

Scheme F



A mixture of **f-1** (0.0005 mol), 3-methyl-benzaldehyde (0.0006 mol), BH_3CN on solid support (0.0006 mol) and acetic acid (8 drops) in CH_3OH (10ml) was stirred at room temperature for 24 hours. The solid support was filtered and washed with CH_3OH. The filtrate was evaporated. The residue (0.53g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 92/8/0.5 to 89/10/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.11g) was crystallized from CH_3OH/disopropylether. The precipitate was separated and dried, yielding 0.072g of compound **f-2**, i.e. 6-methyl-2-[6-(3-methyl-benzylamino)-2-(1-methyl-piperidin-4-ylamino)-benzoimidazol-1-ylmethyl]-pyridin-3-ol (28%, melting point: 240°C).

Scheme G



A mixture of **g-1** (0.0079 mol), **g-2** (0.0095 mol) and triethylamine (0.0118 mol) in dimethylformamide (60ml) was stirred at 80°C for 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2/H_2O. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (7g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.5; 15-40μm). The pure fractions were collected and the solvent was evaporated, yielding 1.2g of intermediate **g-3** (30%).

A mixture of **g-3** (0.0023 mol) and MnO_2 (2.4g) in CH_2Cl_2 (80ml) was stirred at room temperature for 12 hours, and then filtered over celite. Celite was washed with H_2O. The filtrate was evaporated till dryness. The residue (1.2g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1; 35-70μm). The pure fractions were collected and the solvent was evaporated, yielding 0.8g of intermediate **g-4** (67%).

Diethyl benzyl phosphonate (0.0023 mol) was added to a mixture of NaH (0.0047 mol) in tetrahydrofuran (20ml) at 5°C under N_2 flow. The mixture was stirred at 5°C for 30

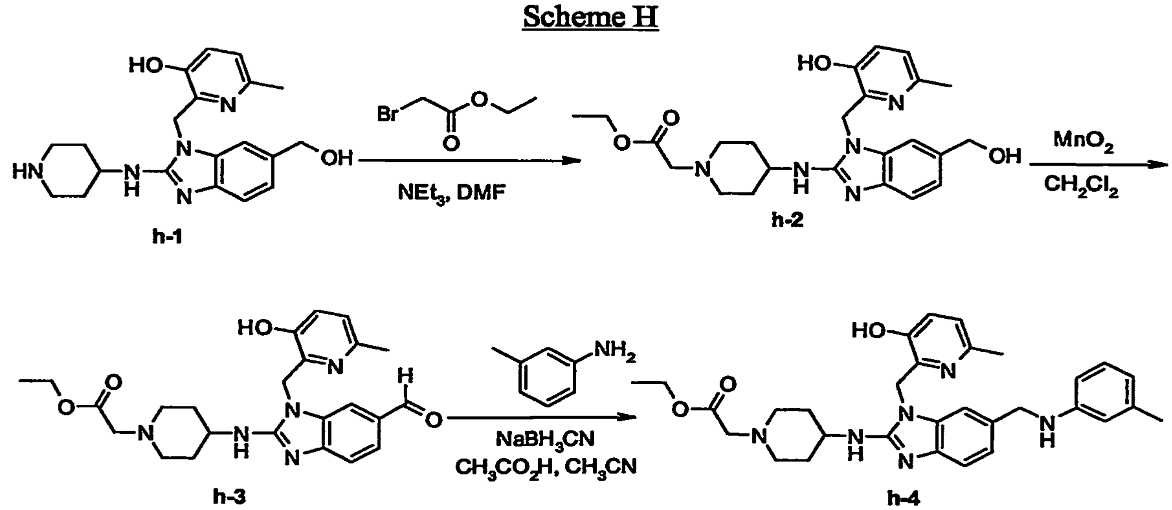
minutes. A solution of g-4 (0.0007 mol) in tetrahydrofuran (10ml) was added drop wise. The mixture was stirred at 5°C for 1 hour, and then stirred at room temperature for 12 hours. H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was crystallized from CH_3OH/2-propanone. The precipitate was filtered off and dried, yielding 0.24g of intermediate g-5 (52%).

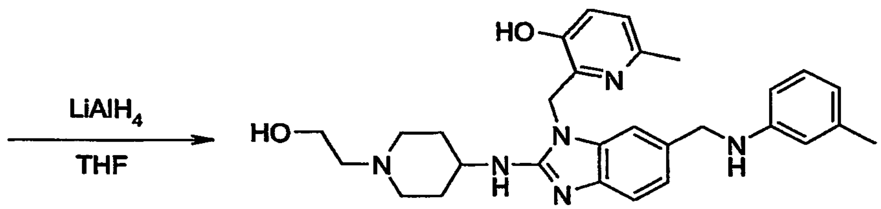
A mixture of g-5 (0.0001 mol) in a 5N solution of HCl in 2-propanol (0.5ml) and 2-propanol (5ml) was stirred at 60°C for 4 hours, and then cooled to room temperature. The precipitate was filtered, washed with 2-propanol/diisopropylether and dried, yielding 0.058g of 2-{2-[1-(2-Amino-ethyl)-piperidin-4-ylamino]-6-styryl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol hydrochloride salt (g-6; 63%, 3.69 HCl + 3.03 H_2O, melting point: > 260°C).

A mixture of g-5 (0.0002 mol) and Pd/C 10% (0.03g) in CH_3OH (10ml) and tetrahydrofuran (10ml) was hydrogenated at room temperature for 4 hours under a 2 bar pressure, and then filtered over celite. Celite was washed with H_2O. The filtrate was evaporated till dryness, yielding 0.14g of intermediate g-7 (100%). This product was used directly in the next reaction step.

A mixture of g-7 (0.0002 mol) in a 5N solution of HCl in 2-propanol (1.4ml) and 2-propanol (15ml) was stirred at 60°C for 4 hours, and then cooled to room temperature. The precipitate was filtered, washed with 2-propanol/diisopropylether and dried, yielding 0.138g of 2-{2-[1-(2-amino-ethyl)-piperidin-4-ylamino]-6-phenethyl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol hydrochloride salt (87%, 3.62 HCl + 2.41 H_2O, melting point: 181°C).

Scheme H





h-5

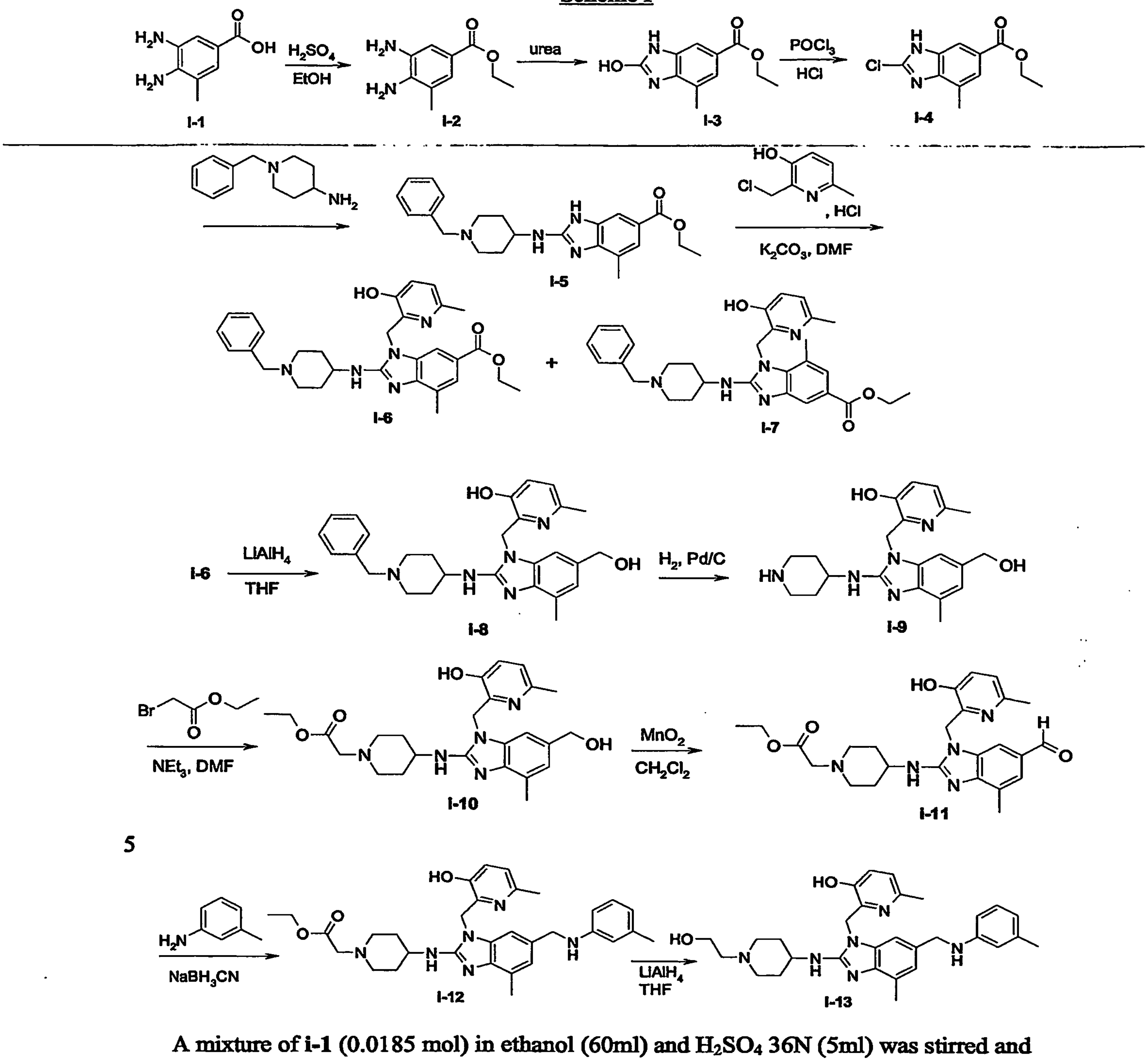
A mixture of **h-1** (0.0027 mol), ethyl-bromo acetate (0.0032 mol) and triethylamine (0.004 mol) in dimethylformamide (40ml) was stirred at 50°C for 1 hour, poured out into ice water and extracted three times with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was taken up in 2-propanone/diisopropylether. The precipitate was filtered, washed with H_2O and dried, yielding 1g of intermediate **h-2** (82%).

Intermediate **h-3** was prepared analogous to the procedure descrbed for the preparation of **g-4.**

CH_3CO_2H (0.2ml) was added at room temperature to a mixture of **h-3** (0.0004 mol), 3-methyl-aniline (0.0005 mol) and $NaBH_3CN$ (0.0005 mol) in CH_3CN (20ml). The mixture was stirred at room temperature for 6 hours. CH_3CO_2H (0.2ml) was added. The mixture was stirred at room temperature for 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2/K_2CO_3 10%. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness, yielding 0.22g of intermediate **h-4**(100%). This product was used directly in the next reaction step.

$LiAlH_4$ (0.0008 mol) was added to a mixture of **h-4** (0.0004 mol) in tetrahydrofuran (20ml) at 5°C under N_2 flow. The mixture was stirred at 5°C for 1 hour, then brought to room temperature and stirred for 4 hours. A minimum of H_2O and then CH_2Cl_2 were added. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.22g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1; 15-40μm). The pure fractions were collected and the solvent was evaporated. The residue (0.1g, 50%) was crystallized from CH_3OH/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.08g of 2-[2-[1-(2-hydroxy-ethyl)-piperidin-4-ylamino]-6-(m-tolylamino-methyl)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (40%, melting point: 137°C).

Scheme I



A mixture of **i-1** (0.0185 mol) in ethanol (60ml) and H_2SO_4 36N (5ml) was stirred and refluxed for 24 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2. The organic layer was washed with a 10% solution K_2CO_3 in water, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness, yielding 3.2g of intermediate **i-2** (89%).

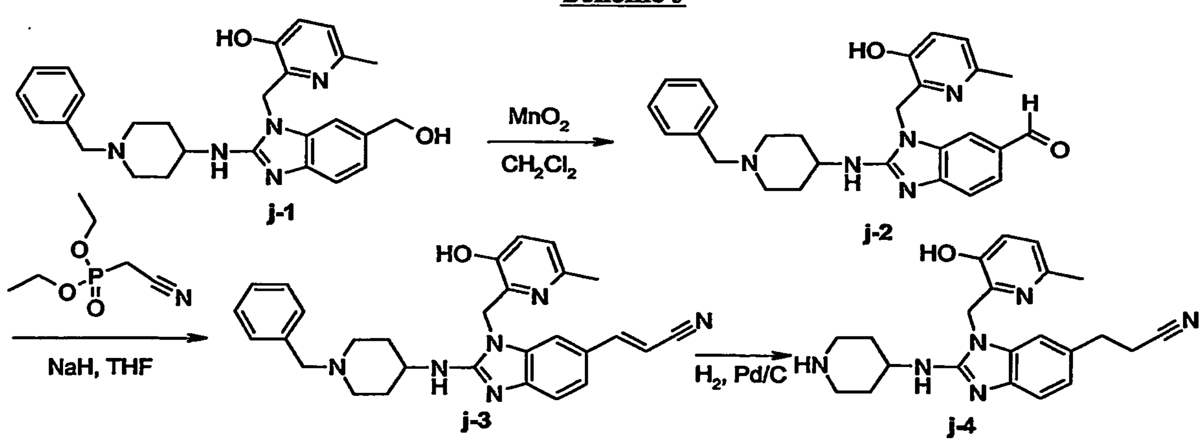
Intermediate **i-3** was prepared in an analogous way to the procedure described for intermediate **a-2.** Intermediate **i-4** was prepared in an analogous way to the procedure described for intermediate **a-3.** Intermediate **i-5** was prepared in an analogous way to the procedure described for intermediate **a-5.**

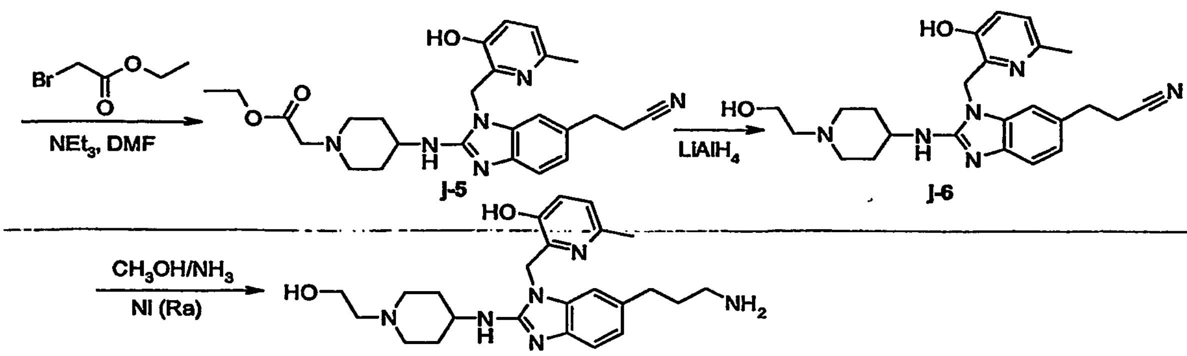
A mixture of **i-5** (0.0048 mol), 2-chloromethyl-6-methyl-3-pyridinol (0.0058 mol) and K_2CO_3 (0.0192 mol) in dimethylformamide (20ml) was stirred at room temperature for 12 hours, poured out into ice water and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (3.4g) was purified by column chromatography over silica gel (eluent: toluene/2-propanol/NH_4OH 83/16/1; 15-35μm). Two fractions were collected and the solvent was evaporated, yielding 0.9g of intermediate **i-6** (37%) and 0.78g of intermediate **i-7** (32%).

Intermediate **i-8** was prepared in an analogous way to the procedure described for intermediate **a-9.** Intermediate **i-9** was prepared in an analogous way to the procedure described for intermediate **a-11.** Intermediate **i-10** (melting point: 221°C) was prepared in an analogous way to the procedure described for intermediate **h-2.** Intermediate **i-11** was prepared in an analogous way to the procedure described for intermediate **h-3.** Intermediate **i-12** (melting point: 143°C) was prepared in an analogous way to the procedure described for intermediate **h-4.**

2-[2-[1-(2-Hydroxy-ethyl)-piperidin-4-ylamino]-4-methyl-6-(m-tolylamino-methyl)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (melting point: 123°C) was prepared in an analogous way to the procedure described for compound **h-5.**

Scheme J





j-7

Intermediate **j-2** was prepared in an analogous way to the procedure described for intermediate **h-3.**

Diethyl cyanomethyl phosphonate (0.0052 mol) was added to a mixture of NaH (0.0105 mol) in tetrahydrofuran (30ml) at 5°C under N_2 flow. The mixture was stirred at 5°C for 30 minutes. A solution of **j-2** (0.0017 mol) in tetrahydrofuran (20ml) was then added. The mixture was stirred at 5°C for 1 hour, and then stirred at room temperature for 12 hours. H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1; 70-200μm). The pure fractions were collected and the solvent was evaporated, yielding 0.7g of intermediate **j-3** (84%).

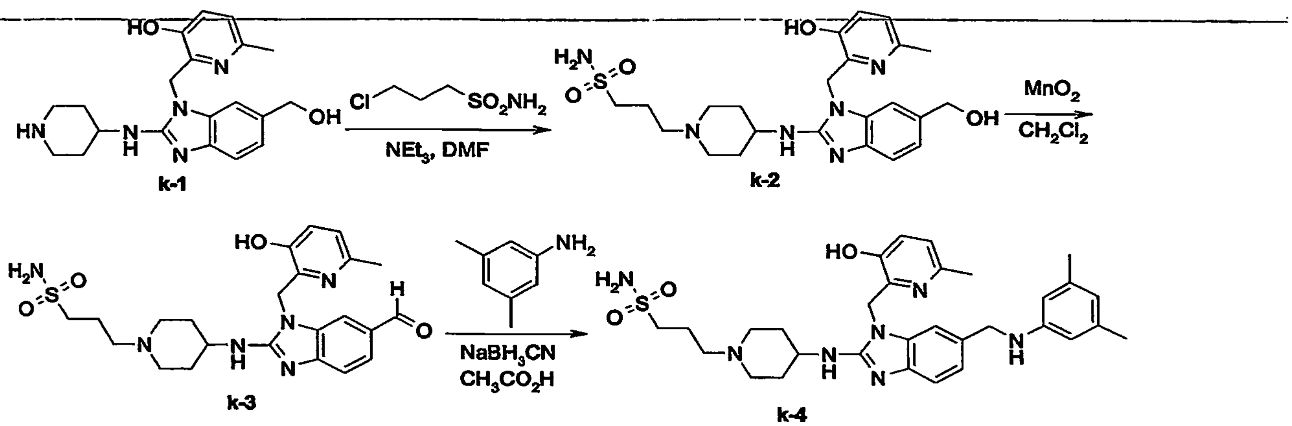
A mixture of **j-3** (0.0014 mol) and Pd/C 10% (0.25g) in CH_3OH (35ml) was hydrogenated at 40°C for 6 hours under an 8 bar pressure, then cooled to room temperature and filtered over celite. The filtrate was evaporated till dryness, yielding 0.3g intermediate **j-4** (52%).

Intermediate **j-5** was prepared in an analogous way to the procedure described for intermediate **h-2.** Intermediate **j-6** (melting point: 207°C) was prepared in an analogous way to the procedure described for intermediate **i-13.**

A mixture of **j-6** (0.0003 mol) and Raney Nickel (0.2g) in a saturated solution of NH_3 in CH_3OH (25ml) was hydrogenated at room temperature for 1 hour, and then filtered over celite. The filtrate was evaporated till dryness. The residue (0.22g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 80/20/2; 10μm). The pure fractions were collected and the solvent was evaporated. The residue (0.083g, 49%) was dissolved in ethanol/2-propanone and converted into the hydrochloric acid salt. The precipitate was filtered off and dried. The residue was crystallized from diisopropylether. The precipitate was filtered off and dried, yielding

0.08g of 2-{6-(3-Amino-propyl)-2-[1-(2-hydroxy-ethyl)-piperidin-4-ylamino]-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol hydrochloride salt (36%, 3.6 HCl, melting point: 185°C).

Scheme K



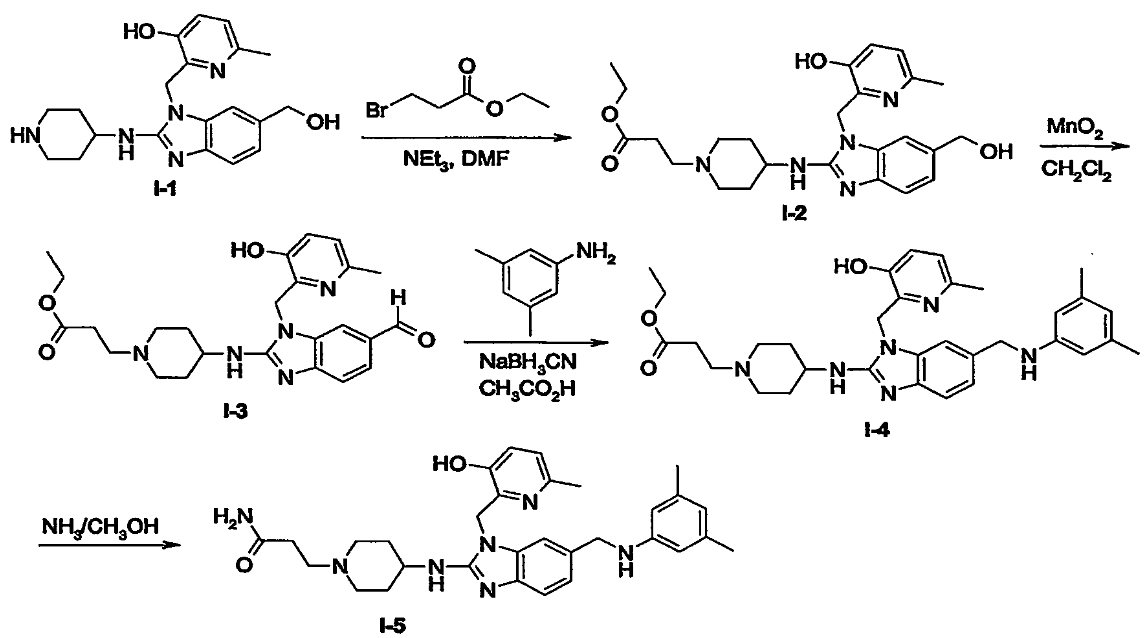
A mixture of k-1 (0.0019 mol), 3-chloro-propylsulfonamide (0.0022 mol) and triethylamine (0.0028 mol) in dimethylformamide (50ml) was stirred at 70°C for 48 hours, poured out into ice water, saturated with K_2CO_3 (powder) and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (1.5g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/2; 15-40μm). The pure fractions were collected and the solvent was evaporated, yielding 0.336g of intermediate k-2 (36%).

A mixture of k-2 (0.0007 mol) and MnO_2 (1g) in CH_2Cl_2 (30ml) was stirred at room temperature for 6 hours, and then filtered over celite. Celite was washed with H_2O. The solvent of the filtrate was evaporated till dryness, yielding 0.33g of intermediate k-3 (100%). This product was used directly in the next reaction step.

CH_3CO_2H (0.2ml) was added at room temperature to a mixture of k-3 (0.0004 mol), 3,5-dimethyl-aniline (0.0005 mol) and $NaBH_3CN$ (0.0005 mol) in CH_3CN (20ml). The mixture was stirred at room temperature for 30 minutes. CH_3CO_2H (0.2ml) was added. The mixture was stirred at room temperature for 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2. The organic layer was washed with a 10% solution of K_2CO_3 in water, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.26g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/1; 5μm). The pure fractions were collected and the solvent was evaporated, yielding 0.09g (32%). This fraction was

crystallized from CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.083g of 2-{4-[6-[(3,5-Dimethyl-phenylamino)-methyl]-1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-1H-benzoimidazol-2-ylamino]-piperidin-1-yl}-ethane-sulfonic acid amide (30%, melting point: 142°C).

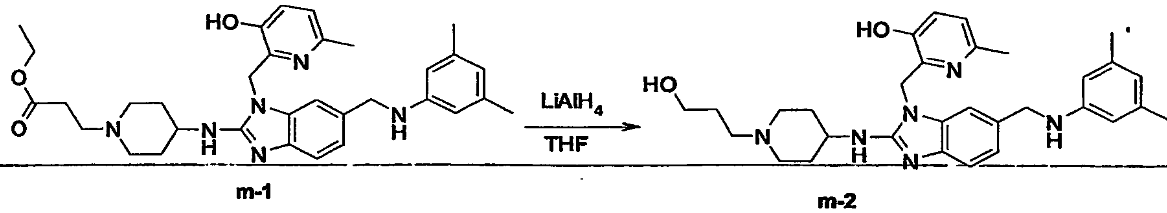
Scheme L



Intermediate l-2 (melting point: 210°C) was prepared in an analogous way to the procedure described for intermediate k-2. Intermediate l-3 was prepared in an analogous way to the procedure described for intermediate k-3. Intermediate l-4 was prepared in an analogous way to the procedure described for compound k-4.

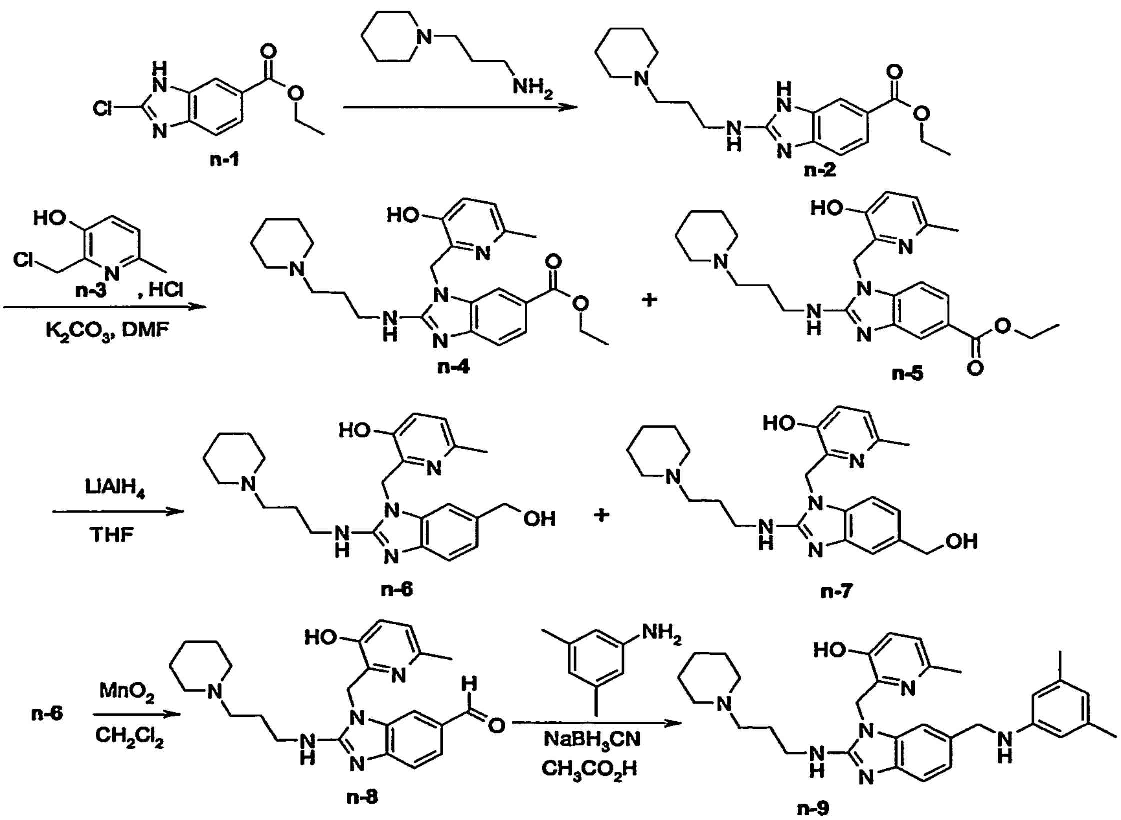
A mixture of l-4 (0.0003 mol) in a 7N solution of NH_3 in CH_3OH (15ml) was stirred at 80°C for 12 hours. The solvent was evaporated till dryness. The residue (0.21g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/14/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.057g, 30%) was crystallized from 2-propanone/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.05g of 2-{4-[6-[(3,5-dimethyl-phenylamino)-methyl]-1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-1H-benzoimidazol-2-ylamino]-piperidin-1-yl}-acetamide (26%, melting point: 206°C).

Scheme M



A mixture of **m-1** (0.0002 mol) in tetrahydrofuran (30ml) was cooled to 5°C under N_2 flow. $LiAlH_4$ (0.0007 mol) was added. The mixture was stirred at 5°C for 1 hour, and then stirred at room temperature for 1 hour. A minimum of H_2O was added. CH_2Cl_2 was added. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.16g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1; 10μm). The pure fractions were collected and the solvent was evaporated. The residue (0.073g, 53%) was crystallized from 2-propanone/CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.064g of 2-{6-[(3,5-dimethyl-phenylamino)-methyl]-2-[1-(2-hydroxy-ethyl)-piperidin-4-ylamino]-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (46%, melting point: 144°C).

Scheme N



A mixture of **n-1** (0.022 mol) and N-(propylamino)-piperidine (0.0207 mol) was stirred at 140°C for 1 hour, and then taken up in CH_2Cl_2/CH_3OH. The organic layer was washed with K_2CO_3 10%, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 92/8/1; 70-200μm). The pure fractions were collected and the solvent was evaporated, yielding 2.2g of intermediate **n-2** (30%).

A mixture of **n-2** (0.0066 mol), **n-3** (0.0073 mol) and K_2CO_3 (0.02 mol) in dimethylformamide (25ml) was stirred at room temperature for 24 hours, poured out into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue was taken up in CH_3CN/diisopropylether. The precipitate was filtered, washed with H_2O and dried, yielding 1.8g of the mixture of intermediates **n-4 and n-5** (61%).

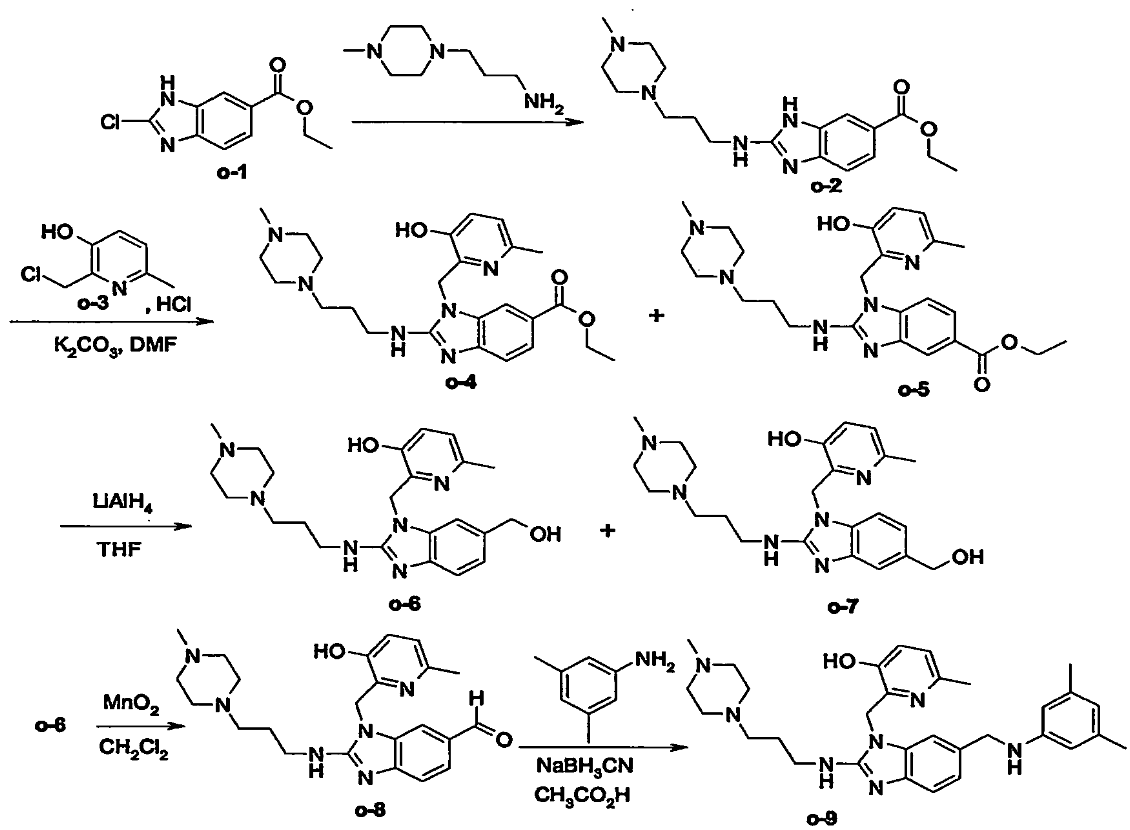
$LiAlH_4$ (0.012 mol) was added portion wise to a mixture of **n-4** (0.002 mol) and **n-5** (0.002 mol) in tetrahydrofuran (60ml) at 5°C under N_2 flow. The mixture was stirred at 5°C for 1 hour, then at room temperature for 12 hours. A minimum of H_2O was added. A solution of CH_2Cl_2/CH_3OH (90/10) was added. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (1.65g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 80/20/3; 15-40μm). Two fractions were collected and the solvent was evaporated, yielding 0.35g of fraction 1 and 0.049g of fraction 2. Fraction 1 was crystallized from 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.33g of intermediate **n-6** (19%, melting point: 220°C). Fraction 2 was crystallized from 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.43g of intermediate **n-7** (26%, melting point: 146°C).

A mixture of **n-6** (0.0006 mol) and MnO_2 (0.5g) in CH_2Cl_2 (30ml) was stirred at room temperature for 12 hours, and then filtered over celite. Celite was washed with H_2O. The filtrate was evaporated till dryness, yielding 0.26g of intermediate **n-8** (100%). The compound was used directly in the next reaction step.

CH_3CO_2H (0.3ml) was added to a mixture of **n-8** (0.0006 mol), 3,5-dimethyl-aniline (0.0007 mol) and $NaBH_3CN$ (0.0007 mol) in CH_3CN (30ml). The mixture was stirred at room temperature for 30 minutes. CH_3CO_2H (0.3ml) was added. The mixture was stirred at room temperature for 24 hours. The solvent was evaporated till dryness. The residue was taken up in 2-propanone/HCl 5N/ethanol. The mixture was stirred at 80°C for 12 hours. The solvent was evaporated till dryness. The mixture was extracted with

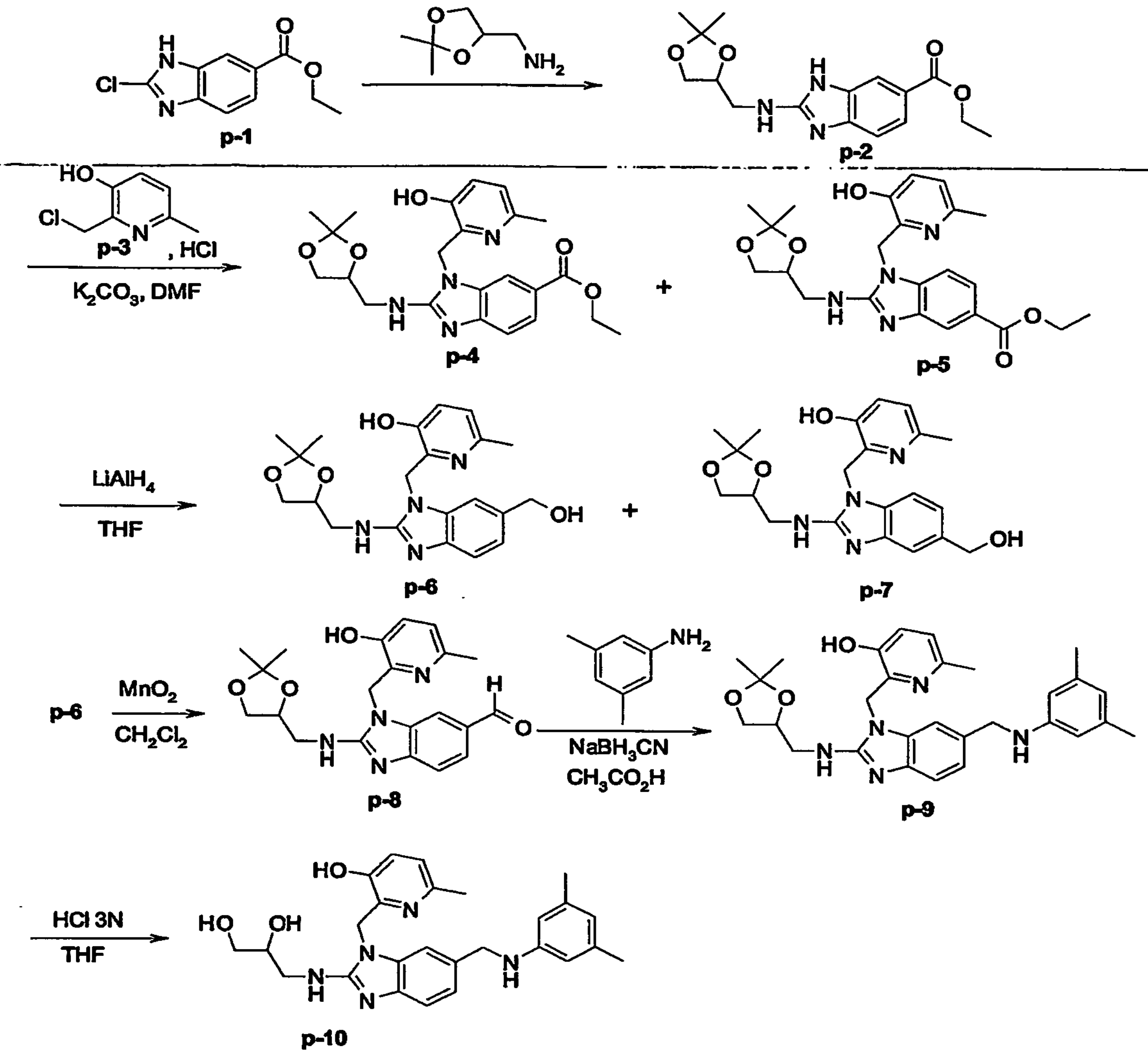
CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.39g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.5; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.119g, 59%) was taken up in CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.17g of 2-[6-[(3,5-dimethyl-phenylamino)-methyl]-2-(3-piperidin-1-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (53%, melting point: 161°C).

Scheme O



2-{6-[(3,5-Dimethyl-phenylamino)-methyl]-2-[3-(4-methyl-piperazin-1-yl)-propylamino]-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (melting point: 150°C) and its intermediates were prepared in an analogous way to the procedures described for preparing compound **n-9.**

Scheme P

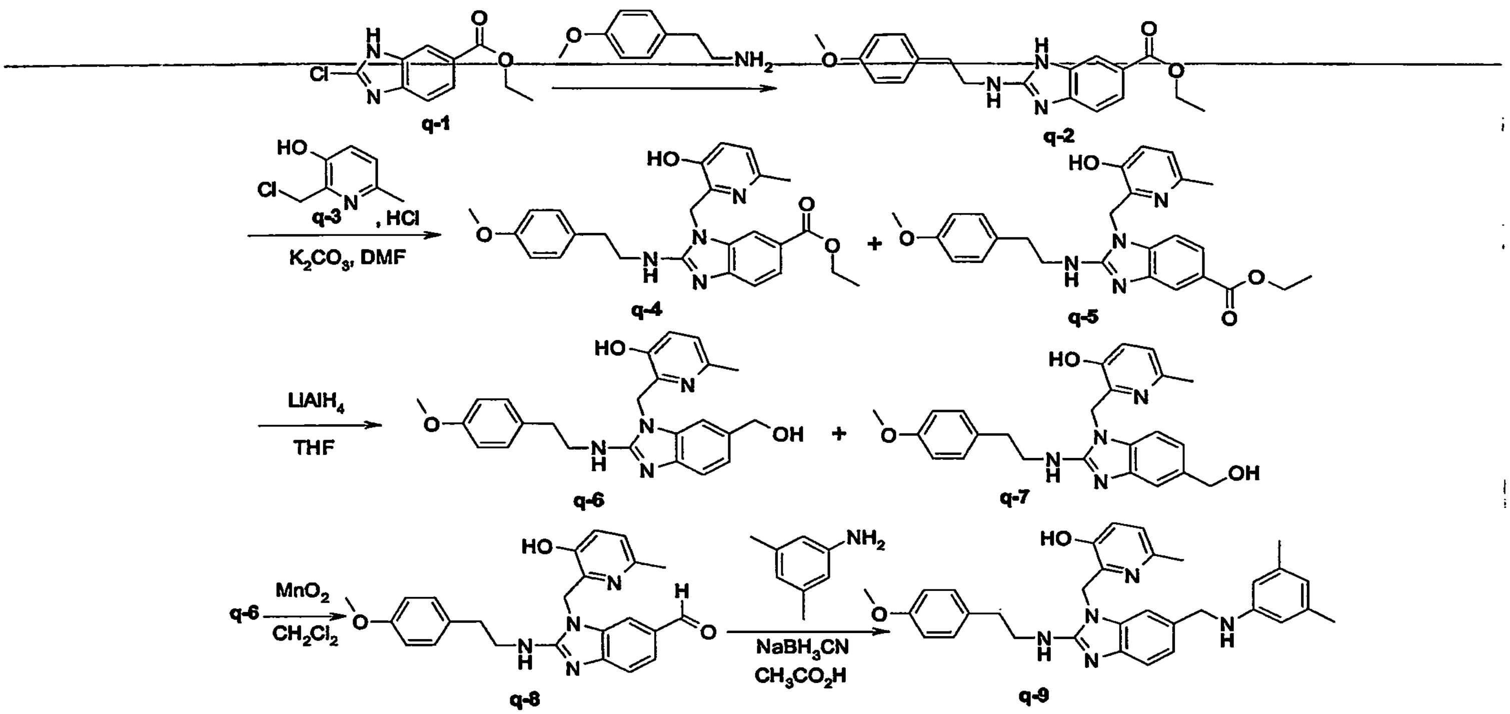


Intermediate **p-9** (melting point: 212°C) was prepared in an analogous way to the procedure described for compound **n-9**.

A mixture of **p-9** (0.0004 mol) in a 3N solution of HCl in water (20ml) and tetrahydrofuran (20ml) was stirred at room temperature for 6 hours, basified with K_2CO_3 (powder) and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.25g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 92/8/0.5; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.17g, 92%) was crystallized from CH_3CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.127g of 3-[6-[(3,5-dimethyl-

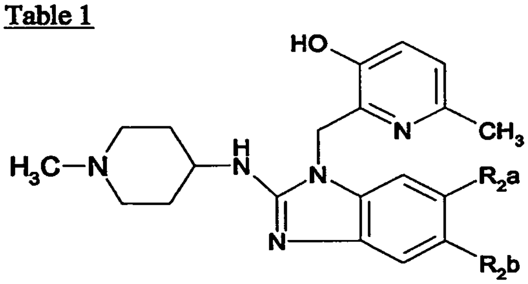
phenylamino)-methyl]-1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-1H-benzoimidazol-2-ylamino]-propane-1,2-diol (69%, melting point: 128°C).

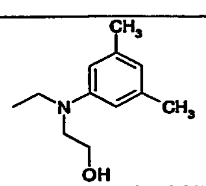
Scheme Q

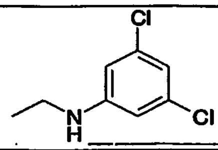
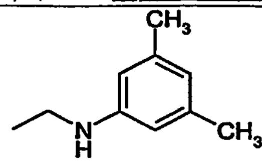
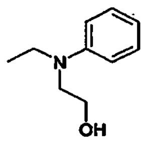
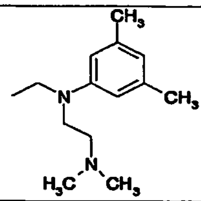
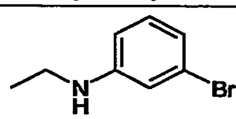
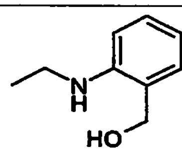
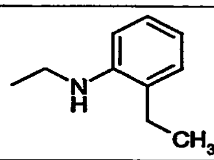
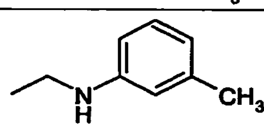
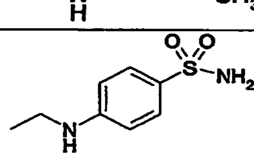
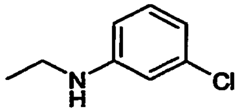
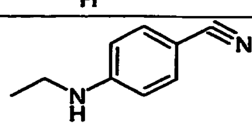


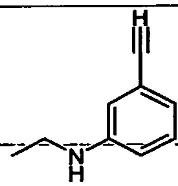
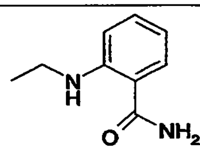
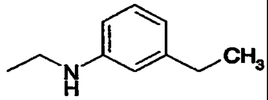
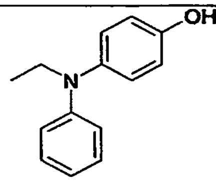
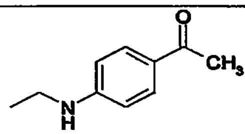
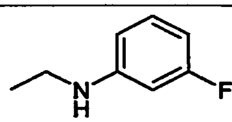
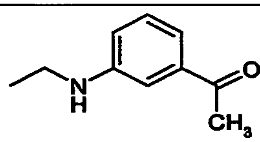
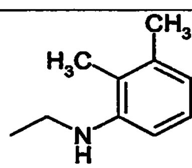
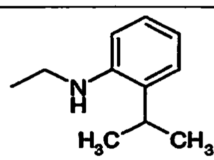
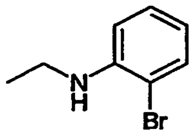
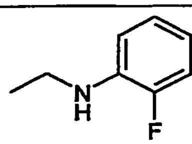
2-{6-[(3,5-Dimethyl-phenylamino)-methyl]-2-[2-(4-methoxy-phenyl)-ethylamino]-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (melting point: 178°C) and its intermediates were prepared in an analogous way to the procedures described for preparing compound **n-9**.

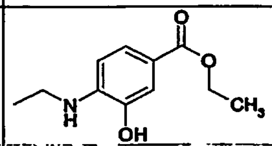
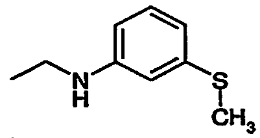
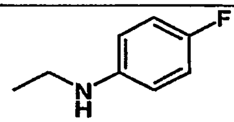
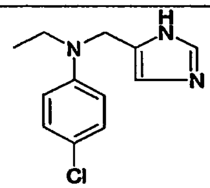
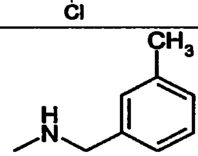
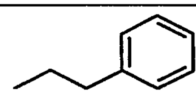
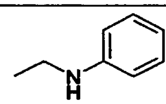
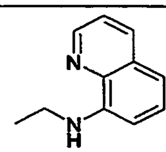
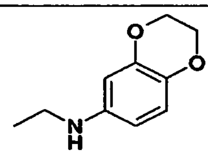
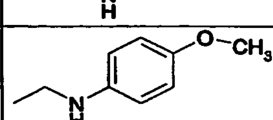
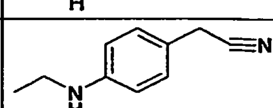
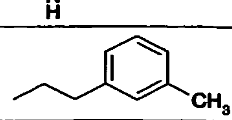
Table 1

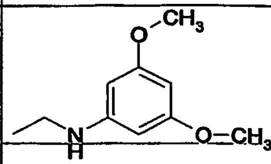
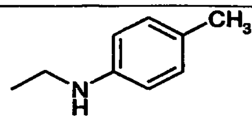
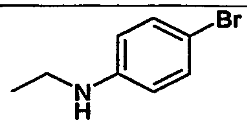
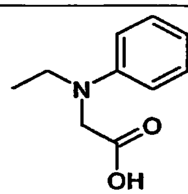
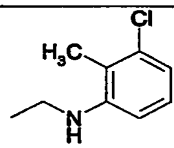
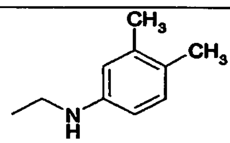
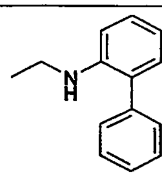
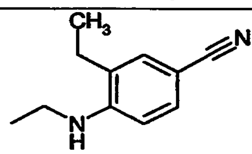
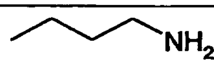
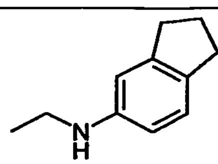
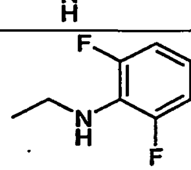


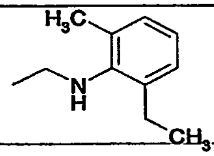
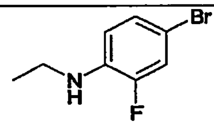
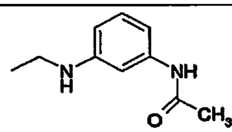
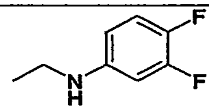
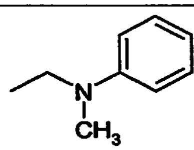
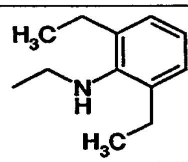
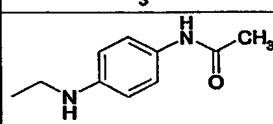
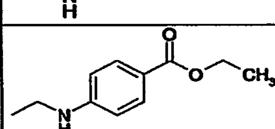
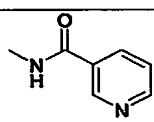
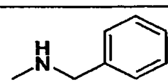
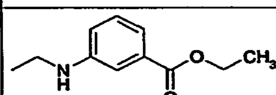
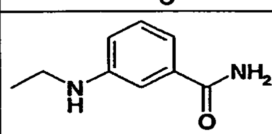
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
1	H		A	529	201°C	A

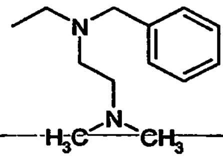
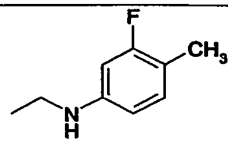
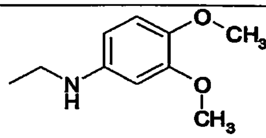
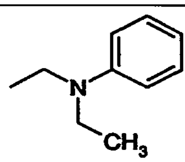
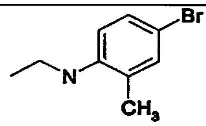
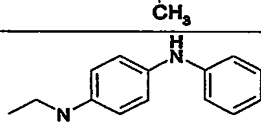
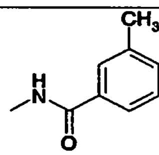
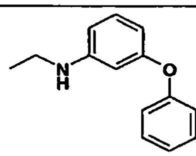
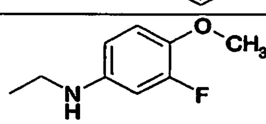
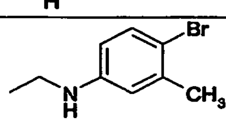
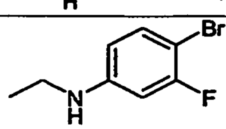
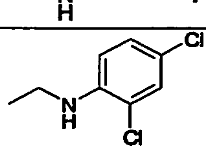
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
2	H		A	525-529	–	B Pathway 1
3	H		A	485	–	B Pathway 1
4	H		A	501	229°C	A
5	H		A	556	199°C	A
6	H		A	535-537	–	B Pathway 1
7	H		A	487	–	B Pathway 1
8	H		A	485	–	B Pathway 1
9	H		A	471	141°C	B Pathway 2
10	H		A	536	–	B Pathway 1
11	H		A	491-493	–	B Pathway 1
12	H		A	482	–	B Pathway 1

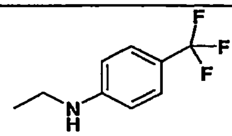
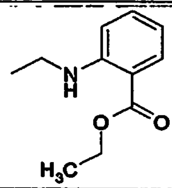
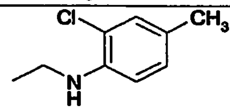
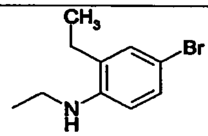
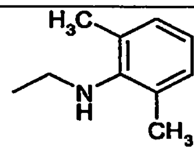
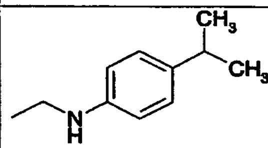
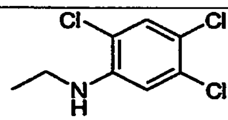
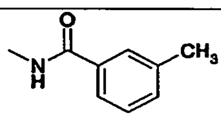
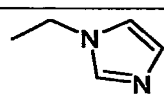
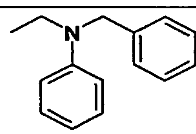
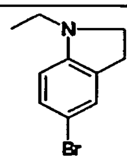
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
13	H		A	481	–	B Pathway 1
14	H		A	500	–	B Pathway 1
15	H		A	485	150°C	B Pathway 2
16	H		A	549	176°C	A
17	H		A	499	–	B Pathway 1
18	H		A	475	130°C	B Pathway 2
19	H		A	499	–	B Pathway 1
20	H		A	485	–	B Pathway 1
21	H		A	499	–	B Pathway 1
22	H		A	535-537	–	B Pathway 1
23	H		A	475	–	B Pathway 1

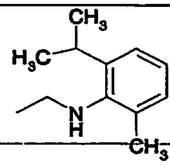
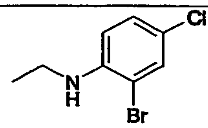
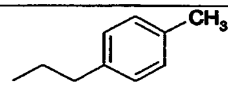
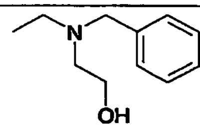
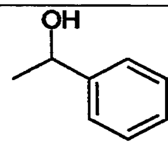
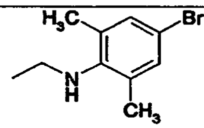
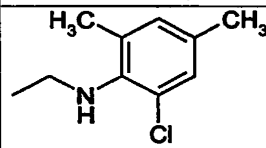
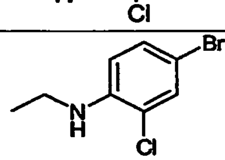
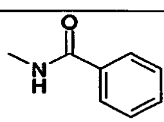
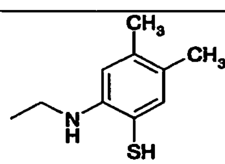
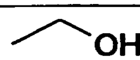
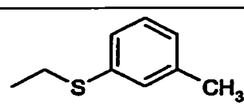
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
24	H		A	545	–	B Pathway 1
25	H		A	503	–	B Pathway 1
26	H		A	475	–	B Pathway 1
27	H		A	571-573	197°C	A
28	H		A	471	240°C	F
29	H		A	456	232°C	G
30	H		A	457	206	B Pathway 2
31	H		A	508	–	B Pathway 1
32	H		A	515	–	B Pathway 1
33	H		A	487	–	B Pathway 1
34	H		A	496	–	B Pathway 1
35	H		A	470		G

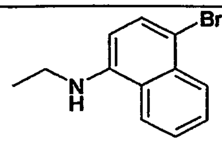
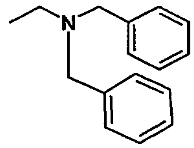
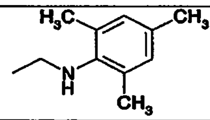
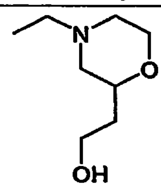
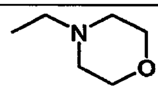
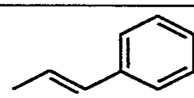
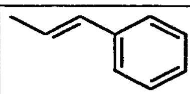
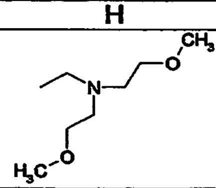
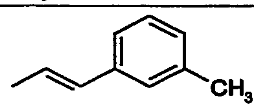
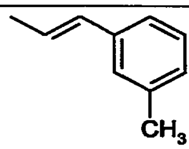
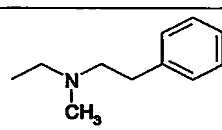
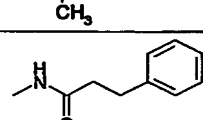
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
36	H		A	517	–	B Pathway 1
37	H		A	471	–	B Pathway 1
38	H		A	535-537	–	B Pathway 1
39	H		A	MH⁻ = 513		A
40	H		A	505-507		B Pathway 1
41	H		A	485	–	B Pathway 1
42	H		A	533	–	B Pathway 1
43	H		A	510	–	B Pathway 1
44	H		A	409	–	J
45	H		A	497	–	B Pathway 1
46	H		A	493	–	B Pathway 1

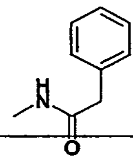
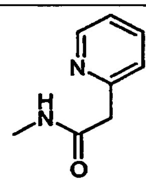
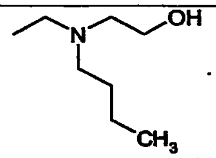
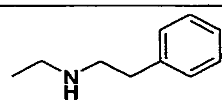
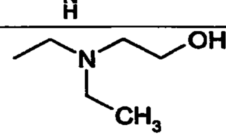
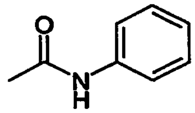
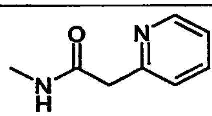
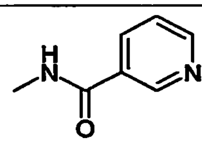
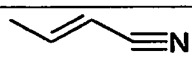
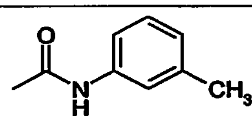
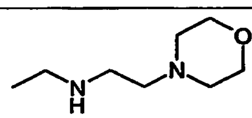
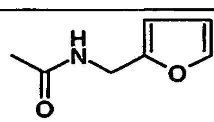
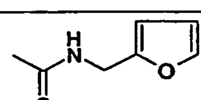
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
47	H		A	499	–	B Pathway 1
48	H		A	553-555	–	B Pathway 1
49	H		A	514	–	B Pathway 1
50	H		A	493	–	B Pathway 1
51	H		A	471	–	B Pathway 1
52	H		A	513	–	B Pathway 1
53	H		A	514	–	B Pathway 1
54	H		A	529	–	B Pathway 1
55		H	A	472	–	E
56	H		A	457	225°C	F
57	H		A	529	205°C	B Pathway 2
58	H		A	500	–	B Pathway 1

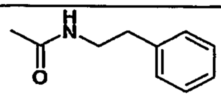
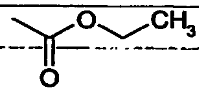
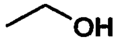
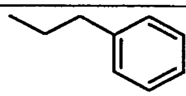
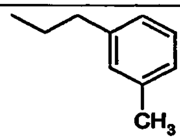
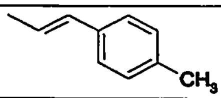
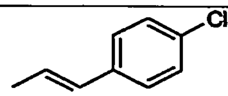
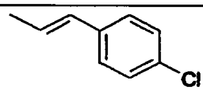
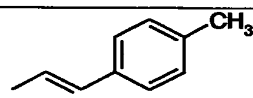
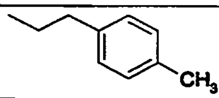
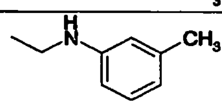
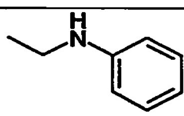
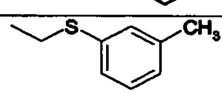
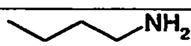
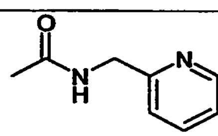
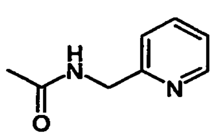
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
59	H		A	542	185°C / HCl salt	A
60	H		A	489	–	B Pathway 1
61	H		A	517	–	B Pathway 1
62	H		A	485	233°C	A
63	H		A	549-551	–	B Pathway 1
64	H		A	548	–	B Pathway 1
65	H		A	485	–	E
66	H		A	549	–	B Pathway 1
67	H		A	505	–	B Pathway 1
68	H		A	549-551	–	B Pathway 1
69	H		A	553-555	–	B Pathway 1
70	H		A	525-529	–	B Pathway 1

Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
71	H		A	525	–	B Pathway 1
72	H		A	529	–	B Pathway 1
73	H		A	505-507	–	B Pathway 1
74	H		A	563-565	–	B Pathway 1
75	H		A	485	–	B Pathway 1
76	H		A	499	–	B Pathway 1
77	H		A	559-565	–	B Pathway 1
78		H	B	485	–	E
79	H		B	432	–	A
80	H		B	547	249°C	A
81	H		B	561-563	184°C	A

Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
82	H		B	513	–	B pathway 1
83	H		B	569-573	–	B Pathway 1
84	H		B	470	224°C	G
85	H		B	515	189°C	A
86	H		B	458	144°C	
87	H		B	563-565	–	B Pathway 1
88	H		B	519-521	–	B Pathway 1
89	H		B	569-573	–	B Pathway 1
90		H	B	471	–	E
91	H		B	517	–	B Pathway 1
92	H		B	382	165°C	A
93	H		B	488	202°C	C

Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
94	H		B	585-587	–	B Pathway 1
95	H		B	547	–	A
96	H		B	499	–	B Pathway 1
97	H		B	495	171°C	A
98	H		B	451	224°C	A
99	H		B	454	262°C	G
100		H	B	454	> 260°C	G
101	H	H	B	352	> 260°C	G
102	H		B	497	–	A
103	H		B	468	244°C	G
104		H	B	468	261°C	G
105	H		B	499	–	A
106	H		B	499	–	E

Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
107	H		B	485	_	E
108	H		B	486	_	E
109	H		B	481	_	A
110	H		C	485	102°C	B Pathway 2
111	H		C	453	_	A
112	H		C	471	169°C	D
113		H	C	486	_	E
114	H		C	472	_	E
115		H	C	403	188°C	J
116	H		C	485	172°C	D
117	H		C	494	161°C	B Pathway 2
118		H	C	475	250°C	D
119	H		C	475	155°C	D

Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
120		H	C	499	200°C	D
~~121~~		~~H~~	~~C~~	~~424~~	~~243°C~~	~~D~~
122		H	C	382	> 260°C	A
123		H	C	456	159°C	G
124		H	C	470	196°C	G
125		H	C	468	229°C	G
126	H		C	488-490	248°C	G
127		H	C	488-490	225°C	G
128	H		C	468	250°C	G
129		H	C	470	222°C	G
130		H	C	471	156°C	B Pathway 2
131		H	C	457	199°C	B Pathway 2
132		H	C	488	208°C	C
133		H	C	409	245°C	J
134	H		C	486	146°C	D
135		H	C	486	230°C	D

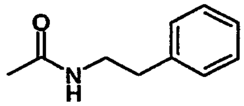
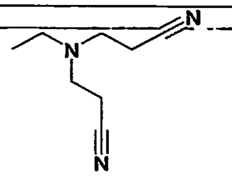
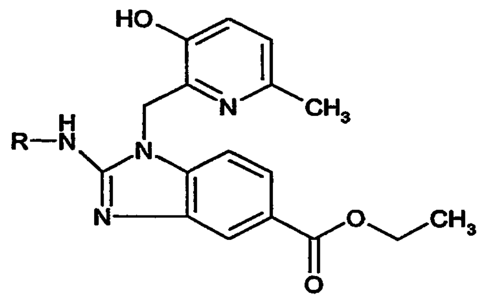
Comp. No.	R2b	R2a	Activity category	Mass (MH+)	Melting point/salt	Synthesis scheme
136	H		C	499	194°C	D
137	H		C	487	–	A

Table 2



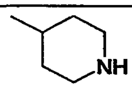
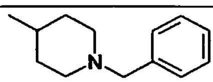
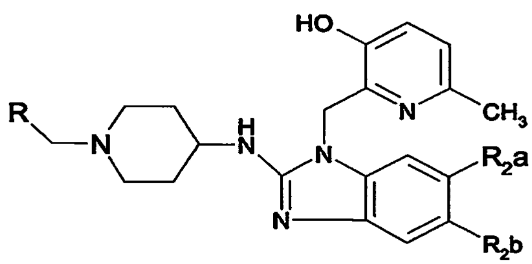
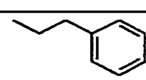
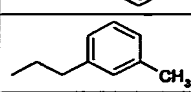
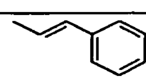
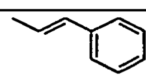
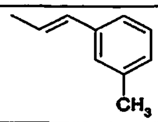
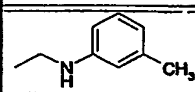
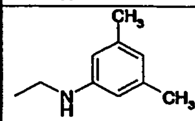
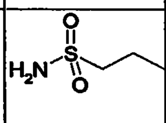
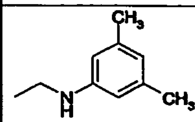
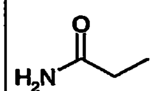
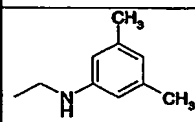
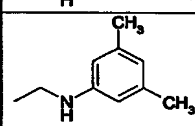
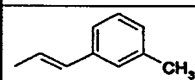
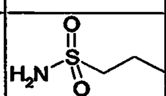
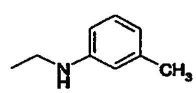
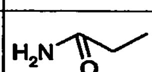
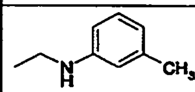
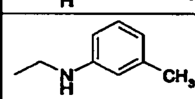
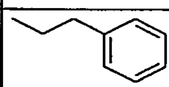
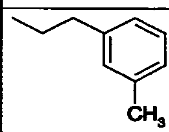
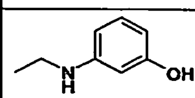
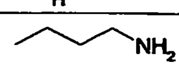
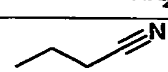
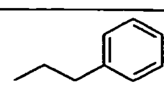
Comp. No.	R	Activity category	Mass (MH+)	Melting point/ salt	Synthesis scheme
138		C	410	164°C	D
139		C	500	227°C	A

Table 3



Comp. No.	R	R2b	R2a	Activity category	Mass (MH+)	Melting point/ salt	Synthesis scheme
140	$-CH_2-NH_2$	H		A	485	181°C / HCl	G
141	$-CH_2-NH_2$	H		A	499	188°C / HCl	G
142	$-CH_2-NH_2$		H	A	483	> 260°C / HCl	G
143	$-CH_2-NH_2$	H		A	483	> 260°C / HCl	G

Comp. No.	R	R2b	R2a	Activity category	Mass (MH+)	Melting point/ salt	Synthesis scheme
144	$-CH_2-NH_2$		H	A	497	210°C / HCl	G
145	$-CH_2-OH$	H		A	501	137°C	H
146	$-CH_2-OH$	H		A	515	133°C	H
147		H		A	592	142°C	K
148		H		A	542	206°C	L
149	$-(CH_2)_2-OH$	H		A	529	144°C	M
150	$-CH_2-NH_2$	H		A	513	211°C / HCl	G
151		H		A	578	193°C	K
152		H		A	528	145°C	L
153		H		A	515	–	M
154	H_2N-CH_2-		H	A	485	183°C / HCl	G
155	H_2N-CH_2-		H	A	499	179°C / HCl	G
156	$HO-CH_2-$	H		A	503	158°C	H
157	$HO-CH_2-$	H		A	439	185°C / HCl	J
158	$HO-CH_2-$	H		A	435	207°C	J
159	$HO-CH_2-$	H		A	486	201°C	G

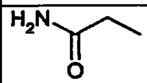
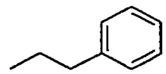
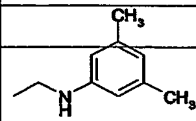
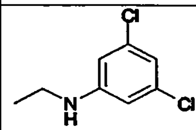
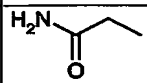
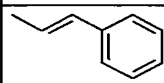
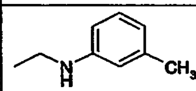
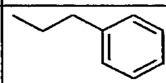
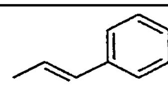
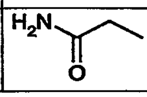
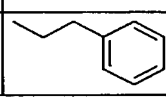
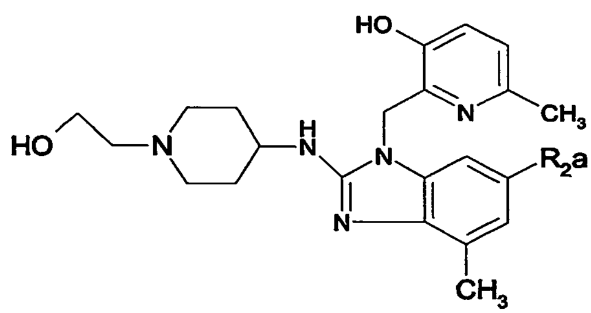
Comp. No.	R	R2b	R2a	Activity category	Mass (MH+)	Melting point/ salt	Synthesis scheme
160		H		A	513	202°C	G
161	phenyl	H		A	561	186°C	H
162	phenyl	H		A	601-605	149°C	H
163			H	B	511	_	G
164	phenyl	H		B	547	198°C	H
165	HO-CH_2-		H	B	486	216°C	G
166	HO-CH_2-	H		B	484	240°C	G
167			H	C	513	160°C	G

Table 4



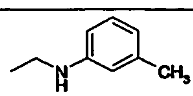
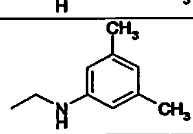
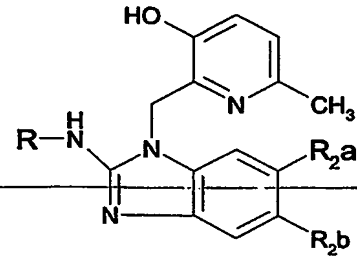
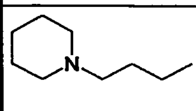
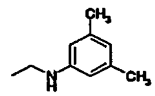
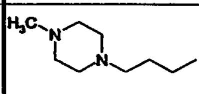
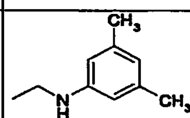
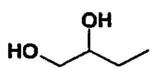
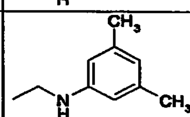
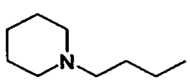
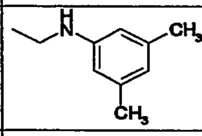
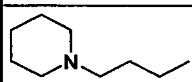
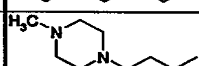
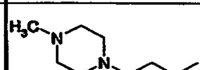
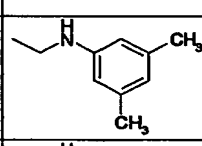
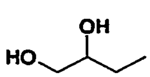
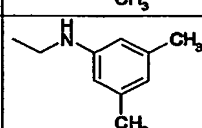
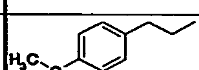
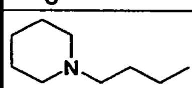
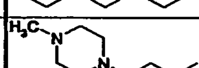
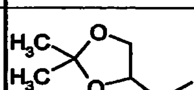
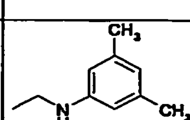
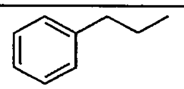
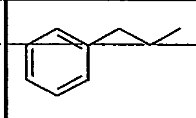
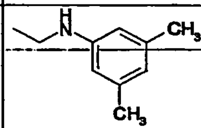
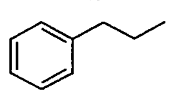
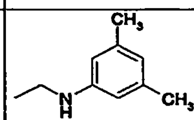
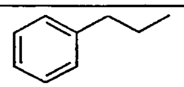
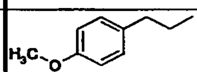
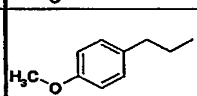
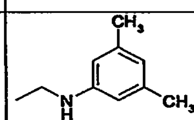
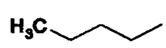
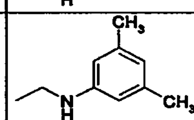
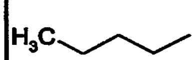
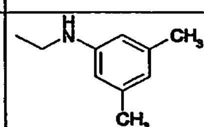
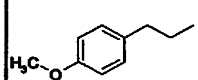
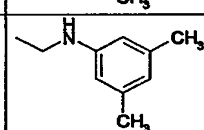
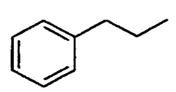
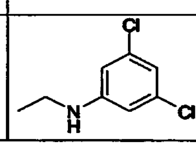
Comp. No.	R2a	Activity category	Mass (MH+)	Melting point/ salt	Synthesis scheme
168		8.5 A	515	123°C	I
169		8.5 A	515	123°C	I

Table 5



Comp. No.	R	R2b	R2a	Activity category	Mass (MH+)	Melting point/ salt	Synthesis scheme
170		H		A	513	161°C	N
171		H		A	528	150°C	O
172		H		A	462	128°C	P
173			H	A	513	182°C	N
174		H	$-CH_2-OH$	A	410	220°C	N
175		H	$-CH_2-OH$	B	425	230°C	O
176			H	B	528	193°C	O
177			H	C	462	215°C	P
178		H	$-CH_2-OH$	C	419	194°C	Q
179		$-CH_2-OH$	H	C	410	146°C	N
180		$-CH_2-OH$	H	C	425	154°C	O
181		H		C	502	212°C	P

Comp. No.	R	R2b	R2a	Activity category	Mass (MH+)	Melting point/ salt	Synthesis scheme
182		$-CH_2-OH$	H	C	389	230°C	Q
183			H	C	492	175°C	Q
184		H		C	492	190°C	Q
185		H	$-CH_2-OH$	C	389	185°C	Q
186		$-CH_2-OH$	H	C	419	185°C	Q
187		H		C	522	178°C	Q
188		H		C	444	181°C	Q
189			H	C	444	237°C	Q
190			H	C	522	196°C	Q
191		H		C	532-536	211°C	Q

B. In vitro screening for activity against Respiratory Syncytial Virus.

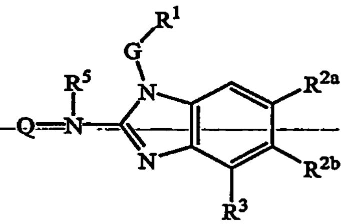
The percent protection against cytopathology caused by viruses (antiviral activity or IC_{50}) achieved by tested compounds and their cytotoxicity (CC_{50}) are both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC_{50} (cytotoxic dose for 50% of the cells) by the IC_{50} (antiviral activity for 50 % of the cells). The tables in the above experimental part list the category to which each of the prepared compounds belong : Compounds belonging to activity category "A" have an pIC_{50} (-log of IC_{50} when expressed in molar units) equal to or more than 7. Compounds belonging to activity

category "B" have a pIC50 value between 6 and 7. Compounds belonging to activity category "C" have a pIC50 value equal to or below 6.

Automated tetrazolium-based colorimetric assays were used for determination of IC_{50} and CC_{50} of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100 $TCID_{50}$ of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row to measure the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4×10^5 cells/ml) of HeLa cells was added to all wells in a volume of 50µl. The cultures were incubated at 37°C in a 5% CO_2 atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 µl of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added . The trays were further incubated at 37°C for 2 hours, after which the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 µl 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

Claims

1. A compound having the formula

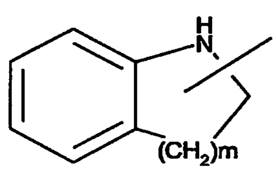


a prodrug, N-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof wherein

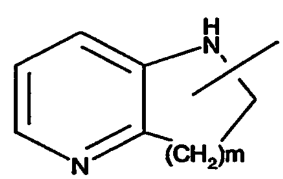
Q is Ar^2, R^6, pyrrolidinyl substituted with R^6, piperidinyl substituted with R^6 or homopiperidinyl substituted with R^6,

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one or more substituents individually selected from the group consisting of hydroxy, C_{1-6}alkyloxy, Ar^1C_{1-6}alkyloxy, C_{1-6}alkylthio, Ar^1C_{1-6}alkylthio, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$ and Ar^1C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$;

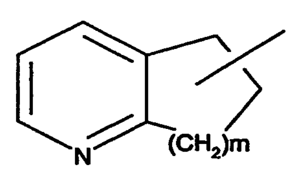
R^1 is Ar^1 or a monocyclic or bicyclic heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-b]pyridyl or a radical of formula



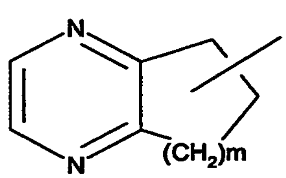
(c-1)



(c-2)



(c-3)



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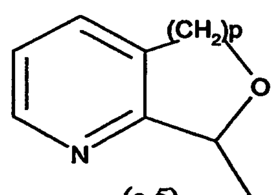

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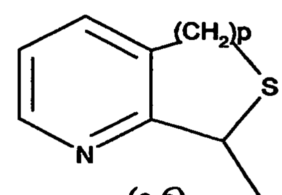

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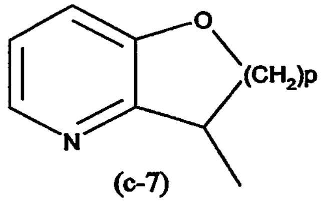
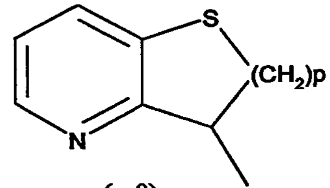

(c-7)


(c-8) ;

wherein each of said monocyclic or bicyclic heterocycles may optionally be substituted with 1 or where possible more, such as 2, 3, 4 or 5, substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

one of R^{2a} and R^{2b} is cyanoC_{1-6}alkyl, cyanoC_{2-6}alkenyl, Ar^3C_{1-6}alkyl, Het^1C_{1-6}alkyl, N($R^{8a}R^{8b}$)C_{1-6}alkyl, Ar^3C_{2-6}alkenyl, Het^1C_{2-6}alkenyl, Ar^3aminoC_{1-6}alkyl, Het^1aminoC_{1-6}alkyl, Ar^3thioC_{1-6}alkyl, Het^1thioC_{1-6}alkyl, Ar^3sulfonylC_{1-6}alkyl, Het^1sulfonylC_{1-6}alkyl, Ar^3aminocarbonyl, Het^1aminocarbonyl, $Ar^3(CH_2)_n$aminocarbonyl, $Het^1(CH_2)_n$aminocarbonyl, Ar^3carbonylamino, Het^1carbonylamino, $Ar^3(CH_2)_n$carbonylamino, $Het^1(CH_2)_n$carbonylamino, and the other one of R^{2a} and R^{2b} is hydrogen;

in case R^{2a} is hydrogen, then R^3 is hydrogen;

in case R^{2b} is hydrogen, the R^3 is hydrogen or C_{1-6}alkyl;

R^{4a} and R^{4b} can be the same or can be different relative to one another, and are each independently hydrogen or C_{1-6}alkyl; or

R^{4a} and R^{4b} taken together may form a bivalent radical of formula -$(CH_2)_s$- wherein s is 4 or 5;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is hydrogen or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of trifluoromethyl, $NR^{7a}R^{7b}$, C_{3-7}cycloalkyl, Ar^2, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, Ar^2-oxy-, Ar^2-thio-, $Ar^2(CH_2)_n$oxy, $Ar^2(CH_2)_n$thio, hydroxycarbonyl, aminocarbonyl, C_{1-4}alkyl-carbonyl, Ar^2carbonyl, C_{1-4}alkoxycarbonyl, $Ar^2(CH_2)_n$carbonyl, aminocarbonyl-oxy, C_{1-4}alkylcarbonyloxy, Ar^2carbonyloxy, $Ar^2(CH_2)_n$carbonyloxy, C_{1-4}alkoxycarbonyl$(CH_2)_n$oxy, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, aminosulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl or a heterocycles selected from the group consisting of

pyrrolidinyl, pyrrolyl, dihydropyrrolyl, thiazolidinyl, imidazolyl, triazolyl, piperidinyl, homopiperidinyl, piperazinyl, pyridyl and tetrahydropyridyl, wherein each of said heterocycle may optionally be substituted with oxo or C_{1-6}alkyl;

R^{7a} is hydrogen, C_{1-6}alkyl, formyl or C_{1-6}alkylcarbonyl;

R^{7b} is hydrogen, C_{1-6}alkyl, formyl or C_{1-6}alkylcarbonyl;

R^{8a} is C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^3C_{1-6}alkyl, Het^1C_{1-6}alkyl;

R^{8b} is C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^3C_{1-6}alkyl, Het^1C_{1-6}alkyl;

each n independently is 1, 2, 3 or 4;

each m independently is 1 or 2;

each p independently is 1 or 2;

Ar^1 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

Ar^2 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from the group consisting of halo, hydroxy, amino, cyano, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy, aminosulfonyl, aminocarbonyl, hydroxycarbonyl, C_{1-4}alkylcarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl and C_{1-4}alkoxycarbonyl;

Ar^3 is phenyl, naphthalenyl, 1,2,3,4-tetrahydro-naphthalenyl or indanyl, wherein said phenyl, naphtyl, 1,2,3,4-tetrahydro-naphthalenyl or indanyl may optionally and each individually be substituted with one or more, such as 2, 3 or 4, substituents selected from the group consisting of halo, hydroxy, mercapto, amino, cyano, C_{1-6}alkyl, Ar^1, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1-oxy, aminosulfonyl, aminocarbonyl, hydroxycarbonyl, C_{1-4}alkylcarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-4}alkylcarbonylamino and C_{1-4}alkoxycarbonyl;

Het^1 is a heterocycle being selected from tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidinonyl, furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, tetrahydroquinolinyl, quinolinyl, isoquinolinyl, benzodioxanyl, benzodioxolyl, indolinyl, indolyl, each of said heterocycle may

optionally be substituted with oxo, amino, Ar^1, C_{1-4}alkyl, aminoC_{1-4}alkyl, Ar^1C_{1-4}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)amino.

2. A compound as claimed in claim 1 wherein G is C_{1-10}alkanediyl

3. A compound according to claim 1 or 2 wherein R^1 is pyridyl optionally substituted with 1 or 2 substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-.

4. A compound as claimed in any one of claim 1 to 3 wherein the compound has the structure of the compound numbers 1 to 77, 140 to 162 or 168 to 174 listed in tables 1 to 5.

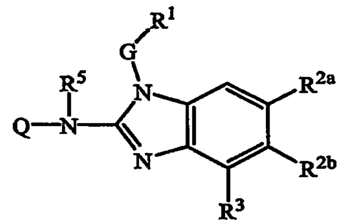
5. A compound as claimed in any one of claims 1 to 4 for use as a medicine.

6. A pharmaceutical compositioncomprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 4.

ABSTRACT

5- OR 6-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS INHIBITORS OF RESPIRATORY SYNCYTIAL VIRUS REPLICATION

The present invention concerns 5- or 6-substituted-benzimidazole derivatives having inhibitory activity on the replication of the respiratory syncytial virus and having the formula



a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof wherein Q is Ar^2, R^6, pyrrolidinyl substituted with R^6, piperidinyl substituted with R^6 or homopiperidinyl substituted with R^6, G is a direct bond or optionally substituted C_{1-10}alkanediyl; R^1 is Ar^1 or a monocyclic or bicyclic heterocycle; one of R^{2a} and R^{2b} is cyanoC_{1-6}alkyl, cyanoC_{2-6}alkenyl, Ar^3C_{1-6}alkyl, Het^1C_{1-6}alkyl, $N(R^{8a}R^{8b})C_{1-6}$alkyl, Ar^3C_{2-6}alkenyl, Het^1C_{2-6}alkenyl, Ar^3aminoC_{1-6}alkyl, Het^1aminoC_{1-6}alkyl, Ar^3thioC_{1-6}alkyl, Het^1thioC_{1-6}alkyl, Ar^3sulfonylC_{1-6}alkyl, Het^1sulfonylC_{1-6}alkyl, Ar^3aminocarbonyl, Het^1aminocarbonyl, $Ar^3(CH_2)_n$amino-carbonyl, $Het^1(CH_2)_n$aminocarbonyl, Ar^3carbonylamino, Het^1carbonylamino, $Ar^3(CH_2)_n$carbonylamino, $Het^1(CH_2)_n$carbonylamino, and the other one of R^{2a} and R^{2b} is hydrogen; in case R^{2a} is hydrogen, then R^3 is hydrogen;
in case R^{2b} is hydrogen, the R^3 is hydrogen or C_{1-6}alkyl. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

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